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FIG.1

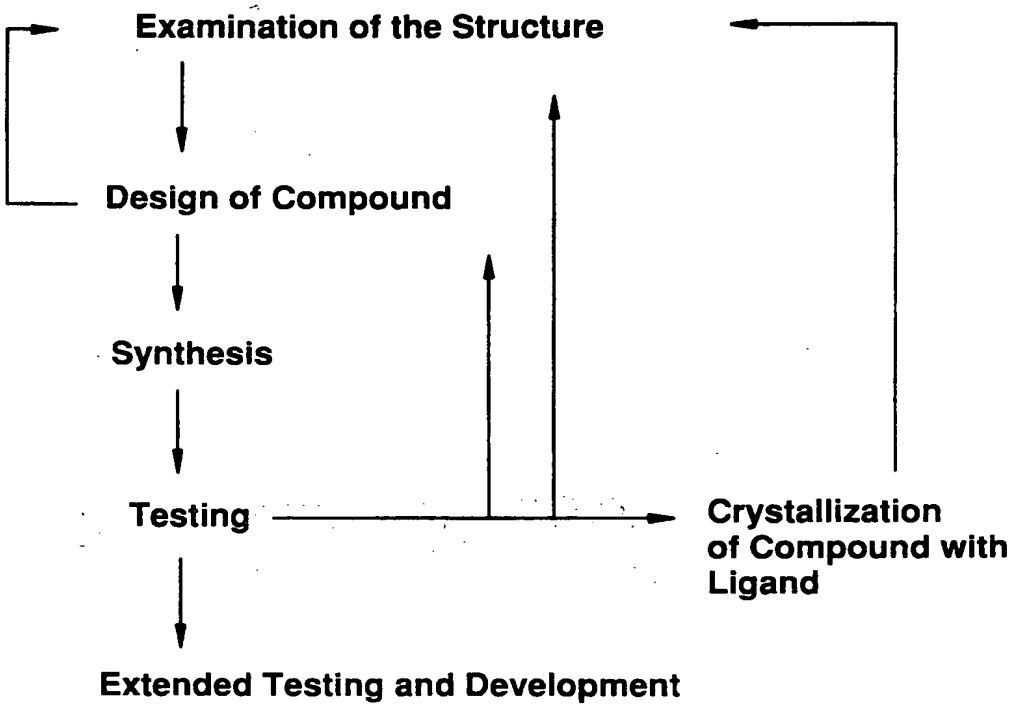


FIG.2

DOMAINS :	NH_2- TERMINAL	DNA BINDING	LIGAND BINDING
HOMOLOGY :	Hypervariable	> 40%	About 20%
FUNCTION :	Transactivation	DNA Binding Dimerization	LIGAND Binding Dimerization Transactivation Nuclear translocation Hsp binding

```
            1                                                          60
   rTRalpha ..... ..... ..... ..... ..... .....
   hTRalpha ..... ..... ..... ..... ..... .....
    hTRbeta ..... ..... ..... ..... ..... .....
  hRARalpha ..... ..... ..... ..... ..... .....
  hRARgamma ..... ..... ..... ..... ..... .....
  hRXRalpha ..... ..... ..... ..... ..... .....
   hRXRbeta ..... ..... ..... ..... ..... .....
 hPPARalpha ..... ..... ..... ..... ..... .....
  hPPARbeta ..... ..... ..... ..... ..... .....
 hPPARgamma ..... ..... ..... ..... ..... .....
       hVDR ..... ..... ..... ..... ..... .....
        hER ..... ..... ..... ..... ..... .....
        hGR ..... ..... ..... ..... ..... .....
        hPR MTELKAKGPR APHVAGGPPS PEVGSPLLCR PAAGPFPGSQ TSDTLPEVSA IPISLDGLLF
        hMR ...METKGYH SLPEGLDMER RWGQVSQAVE RSSLGPTERT DENNYMEIVN VSCVSGAIPN
        hAR ..... ..... ..... ..... ..... .....
```

FIG.3A

```
                61                                                      120
     rTRalpha  .......... .......... .......... .......... .......... ..........
     hTRalpha  .......... .......... .......... .......... .......... ..........
      hTRbeta  .......... .......... .......... .......... .......... ..........
    hRARalpha  .......... .......... .......... .......... .......... ..........
    hRARgamma  .......... .......... .......... .......... .......... ..........
    hRXRalpha  .......... .......... .......... .......... .......... ..........
     hRXRbeta  .......... .......... .......... .......... .......... ..........
   hPPARalpha  .......... .......... .......... .......... .......... ..........
    hPPARbeta  .......... .......... .......... .......... .......... ..........
   hPPARgamma  .......... .......... .......... .......... .......... ..........
         hVDR  .......... .......... .......... .......... .......... ..........
          hER  .......... .......... .......... .......... .......... ..........
          hGR  .......... .......... .....MDSKE SLTPGREENP SSVLAQERGD VMDFYKTLRG
          hPR  PRPCQGQDPS DEKTQDQQSL SDVEGAYSRA EATRGAGGSS SSPPEKDSGL LDSVLDTLLA
          hMR  NSTQGSSKEK QELLPCLQQD NNRPGILTSD IKTELESKEL SATVAESMGL YMDSVRDADY
          hAR  .......... .......... .......... .......... .......... ..........
```

FIG.3B

```
            121                                                       180
   rTRalpha ..... ..... ..... ..... ..... .....
   hTRalpha ..... ..... ..... ..... ..... .....
    hTRbeta ..... ..... ..... ..... ..... .....
  hRARalpha ..... ..... ..... ..... ..... .....
  hRARgamma ..... ..... ..... ..... ..... .....
  hRXRalpha ..... ..... ..... ..... ..... .....
   hRXRbeta ..... ..... ..... ..... ..... .....
 hPPARalpha ..... ..... ..... ..... ..... .....
  hPPARbeta ..... ..... ..... ..... ..... .....
 hPPARgamma ..... ..... ..... ..... ..... .....
       hVDR ..... ..... ..... ..... ..... .....
        hER ..... ..... ..... ..... ..... .....
        hGR GATVKVSASS PSLAVASQS. ..... ..... .DSKQRRLLV DFPKGSVSNA
        hPR PSGPGQSQPS PPACEVTSSW CLFGPELPED PPAAPATQRV LSPLMSRSGC KVGDSSGTAA
        hMR SYEQQNQQGS MSPAKIYQNV EQLVKFYKGN GHRPSTLSCV NTPL..RSFM SDSGSSVNGG
        hAR ..... ..... ..... ..... ..... .....
```

FIG.3C

```
                181                                                       240
      rTRalpha  .......... .......... .......... .......... .......... ..........
      hTRalpha  .......... .......... .......... .......... .......... ..........
       hTRbeta  .......... .......... .......... .......... .......... ..........
     hRARalpha  .......... .......... .......... .......... .......... ..........
     hRARgamma  .......... .......... .......... .......... .......... ..........
     hRXRalpha  .......... .......... .......... .......... .......... ..........
      hRXRbeta  .......... .......... .......... .......... .......... ..........
    hPPARalpha  .......... .......... .......... .......... .......... ..........
     hPPARbeta  .......... .......... .......... .......... .......... ..........
    hPPARgamma  .......... .......... .......... .......... .......... ..........
          hVDR  .......... .......... .......... .......... .......... ..........
           hER  .......... .......... .......... .......... .......... ..........
           hGR  QQPDLSKAVS LSMGLYMGET ETKVMGNDLG FPQQGQISLS SGETDLKLLE ESIANLNRS.
           hPR  AHKVLPRGLS PARQLLLPAS ESPHWSGAPV KPSPQAAAVE VEEEDSSESE ESAGPLLKGK
           hMR  VMRAIVK..S PIMCHEKSPS VCSPLNMTSS VCSPAGINSV SSTTASFGSF PVHSPITQGT
           hAR  .......... .......... .......... .......... .......... ..........
```

FIG.3D

```
            241                                                       300
  rTRalpha  .......... .......... .......... .......... .......... ..........
  hTRalpha  .......... .......... .......... .......... .......... ..........
   hTRbeta  .......... .......... .......... .......... .......... ..........
 hRARalpha  .......... .......... .......... .......... .......... ..........
 hRARgamma  .......... .......... .......... .......... .......... ..........
 hRXRalpha  .......... .......... .......... .......... .......... ..........
  hRXRbeta  .......... .......... .......... .......... .......... ..........
hPPARalpha  .......... .......... .......... .......... .......... ..........
 hPPARbeta  .......... .......... .......... .......... .......... ..........
hPPARgamma  .......... .......... .......... .......... .......... ..........
       hVDR .......... .......... .......... .......... .......... ..........
        hER .......... .......... .......... .......... .......... ..........
        hGR ....TSVPEN PKSSASTAVS AAPTEKEFPK THSDVSSEQQ HLKGQTGTNG GNVKLYTT..
        hPR PRALGGAAAG GGAAACPPGA AAGGVALVPK EDSRFSAPRV ALVEQDAPMA PGRSPLATTV
        hMR PLTCSPNAEN RGSRSHSPAH ASNVGSPLSS PLSSMKSSIS SPPSHCSVKS PVSSPNNVTL
        hAR .......... .......... .......... .......... .......... ..........
```

FIG.3E

```
            301                                                       360
  rTRalpha  .......... .......... .......... .......... .......... ..........
  hTRalpha  .......... .......... .......... .......... .......... ..........
   hTRbeta  .......... .......... .......... .......... .......... ..........
 hRARalpha  .......... .......... .......... .......... .......... ..........
 hRARgamma  .......... .......... .......... .......... .......... ..........
 hRXRalpha  .......... .......... .......... .......... .......... ..........
  hRXRbeta  .......... .......... .......... .......... .......... ..........
hPPARalpha  .......... .......... .......... .......... .......... ..........
 hPPARbeta  .......... .......... .......... .......... .......... ..........
hPPARgamma  .......... .......... .......... .......... .......... ..........
       hVDR  .......... .......... .......... .......... .......... ..........
        hER  .......... .......... .......... .......... .......... ..........
        hGR  .......... ......DQST FDILQDLEFS SGSPGK.... ........ET NESPWRSDLL
        hPR  MDFIHVPILP LNHALLAART RQLLEDESYD GGAGAA.... ........SA FAPPRTSPCA
        hMR  RSSVSSPANI NNSRCSVSSP SNTNNRSTLS SPAASTVGSI CSPVNNAFSY TASGTSAGSS
        hAR  .......... .......... .......... .......... .......... ..........
```

FIG.3F

```
            361                                                        420
  rTRalpha  .......... .......... .......... .......... .......... ..........
  hTRalpha  .......... .......... .......... .......... .......... ..........
   hTRbeta  .......... .......... .......... .......... .......... ..........
 hRARalpha  .......... .......... .......... .......... .......... ..........
 hRARgamma  .......... .......... .......... .......... .......... ..........
 hRXRalpha  .......... .......... .......... .......... .......... ..........
  hRXRbeta  .......... .......... .......... .......MSW AARPPFLPQR HAEGSVGRWG
hPPARalpha  .......... .......... .......... .......... .......... ..........
 hPPARbeta  .......... .......... .......... .......... .......... ..........
hPPARgamma  .......... .......... .......... .......... .......... ..........
      hVDR  .......... .......... .......... .......... .......... ..........
       hER  .......... .......... .......... .......... .......... .......MTM
       hGR  IDENCLLSPL AGEDDSFLLE GNSNEDCKPL ILPDTKPKIK DNGDLVLSSP SNVTLPQVKT
       hPR  SSTPVAVGDF P..DCAYPPD AEPKDDAYPL YSDFQPPALK IKEEEEGAEA SARSPRSYLV
       hMR  TLRDVVPSPD TQEKGAQEVP FPKTEEVESA ISNGVTGQLN IVQYIKPEPD GAFSSSCLGG
       hAR  .......... .......... .......... .......... .......... ..........
```

FIG.3G

```
          421                                                       480
  rTRalpha ..... ..... ..... ..... ..... .....
  hTRalpha ..... ..... ..... ..... ..... .....
   hTRbeta ..... ..... ..... ..... ..... .....
 hRARalpha ..... ..... ..... ..... ..... .....
 hRARgamma ..... ..... ..... ..... ..... .....
 hRXRalpha ..... ..... ..... ..... MDTKHFLPLD FSTQVNSS..
  hRXRbeta AKECIVGSAT ALAGSRSGGG GGGGRRRTTN PGAGARGWTG RDGRH..GRD SRSPDSSSPN
hPPARalpha ..... ..... ..... ..... ..... .....
 hPPARbeta ..... ..... ..... ..... ..... .....
hPPARgamma ..... ..... ..... ..... ..... .....
      hVDR .........M DTEDLPANNA PLTVNEQLLG SCTLKFPAQD AQVIVMSGQE TIRVLEVEVD
       hER TLHTKASGMA LLHQIQGNEL EPLNRPQLKI PLERPLGEVY LDSSKPAVYN YPEGAAYEFN
       hGR EKEDFIELCT PGVIKQEKLG TVYCQASFPG ANIIG..... .....NK MSAISVHGVS
       hPR AGANPAAFPD FPLGPPPPLP PR.ATPSRPG EAAVT..... .....AA PASASVSSAS
       hMR NSKINSDSSF SVPIKQESTK HSCSGTSFKG NPTVNPFPFM DGSYFSFMDD KDYYSLSGIL
       hAR ..... ..... .....GG GGGEA..... .....GA VAPYGYTRP.
```

FIG.3H

```
          481                                                                 540
rTRalpha  ..........  ..........  ..........  ..........  ...MEQKPSK VECGSDPEEN
hTRalpha  ..........  ..........  ..........  ..........  ...MEQKPSK VECGSDPEEN
 hTRbeta  ..........  ..........  ..MTPNSMTE NGLTAWDKPK HCPDREHDWK LVGMSEACLH
hRARalpha ..........  ..........  ..........  ..........  ..........  ..........
hRARgamma ..........  ..........  ..........  .........M ATNKERLFAA GALGPGSGYP
hRXRalpha .LTSPTGR..  GSMAAPSLHP SLGPGIGSPG .QLHSPISTL SSPINGMGPP FSVISSPMGP
 hRXRbeta PLPQGVPP..  PSPPGPPLPP STAPTLGGSG .APPPP....  PMPPPPLGSP FPVISSSMGS
hPPARalpha ..MVDTESPL CPLSPLEAGD LESPLSEEFL QEMGNIQEIS QSIGEDSSGS FGFTEYQYLG
 hPPARbeta ..........  .....MEQPQ EEAP......  .EVREEEEKE EVAEAEGAPE LNGGPQHALP
hPPARgamma ..........  .......MVD TEMPFWPTNF ....GISSVD LSMMDDHSHS FDIKPFTTVD
      hVDR TALSSAGAAE SGGDEEGSGQ SLEATEEAQL DGPVTTSSTT AVTVEVSAPV VQTVVSKAAI
       hER AAAAANAQVY GQTGLPYGPG SEAAAFGSNG LGGFPPLNSV SPSPLMLLHP PPQLSPFLQP
       hGR TSGGQMYHYD MNTASLSQQQ DQ........  .KPIFNVIPP IPVGSEN...  ..........
       hPR SSGSTLECIL YKAEGAPPQQ GPFAPPPCKA PGASGCLLPR DGLPSTS...  ..........
       hMR GPPVPGFDGN CEGSGFPVGI KQEPDDGSYY PEASIPSSAI VGVNSGGQSF HYRIGAQGTI
       hAR ..........  ..PQGLAGQE SDFTAPDVWY PGG...MVSR VPYPSPT...  ..........
```

FIG.3I

```
            541                                                                 600
  rTRalpha  SARSPDGKRK RKN.GQCP.. .....LKSSM .......... .......... ......SGYI
  hTRalpha  SARSPDGKRK RKN.GQCS.. .....LKTSM .......... .......... ......SGYI
   hTRbeta  RKSHSERRST LKN.EQSSPH LIQTTWTSSI FHLDHDDVND QSVSSAQTFQ TEEKKCKGYI
 hRARalpha  .......... .......... ........PN SNHVASGAGE AAIETQSSSS EEIVPSPPSP
 hRARgamma  GAGFPFAFPG ALR.GSPPFE MLSPSFRGLG QPDLPKEMAS LSVETQSTSS EEMVPSSPSP
 hRXRalpha  HSMSVP.... .TTPTLGFST GSPQLSS... .PMNPVSSSE DIKPPLGLNG VLKVPAHPSG
  hRXRbeta  PGLPPP.... .APPGFSGPV SSPQINSTVS LPGGGSGPPE DVKPPVLGVR GLHCPPPPGG
hPPARalpha  SCPGSDGSVI TDTLSPA... .......... .......... .SSPS..SVT YPVVPGSVDE
 hPPARbeta  SSSYTD.... ...LSRS... .......... .......... .SSPP..SLL DQLQMGC.DG
hPPARgamma  FSSISAPHYE DIPFTRADPM VADYKYDLKL QEYQSAIKVE PASPPYYSEK AQLYNRPHEE
      hVDR  SVSPAQQTSV PITVQACPQV LTQDGLASLM TGMLAQQSSL GQPLLIPLSM AGSVGGQGGL
       hER  HGQQVPYYLE NEPSGYTVRE AGPP....AF YRPNSDNRRQ GGRERLASTN DKGSMAMESA
       hGR  ..WNRCQGSG DDNLTSLGTL NFPGRTVFSN GYSSPSMRPD V.......... .SSPPSSSST
       hPR  ..ASAAAAGA APALYPALGL NGLPQLGYQA AVLKEGLPQV YPPYLNYLRP DSEASQSPQY
       hMR  SLSRSARDQS FQHLSSFPPV NTLVESWKSH GDLSSRRSDG YPVLEYIPEN VSSSTLRSVS
       hAR  ..CVKSEMGP WMDSYSG... ......PYGD MRLETARDHV LP..IDYYFP ..........
```

FIG.3J

```
                601                                                        660
      rTRalpha  PSYLDKDEQC VVCGDKATGY HYRCITCEGC KGFFRRTIQK NLHPTYSCKY DS........
      hTRalpha  PSYLDKDEQC VVCGDKATGY HYRCITCEGC KGFFRRTIQK NLHPTYSCKY DS........
       hTRbeta  PSYLDKDELC VVCGDKATGY HYRCITCEGC KGFFRRTIQK NLHPSYSCKY EG........
     hRARalpha  PPLPRIYKPC FVCQDKSSGY HYGVSACEGC KGFFRRSIQK NM..VYTCHR DK........
     hRARgamma  PPPPRVYKPC FVCNDKSSGY HYGVSSCEGC KGFFRRSIQK NM..VYTCHR DK........
     hRXRalpha  NMASFTKHIC AICGDRSSGK HYGVYSCEGC KGFFKRTVRK DL..TYTCRD NK........
      hRXRbeta  PGAG..KRLC AICGDRSSGK HYGVYSCEGC KGFFKRTIRK DL..TYSCRD NK........
    hPPARalpha  SPSGALNIEC RICGDKASGY HYGVHACEGC KGFFRRTIRL KLVYD...KC DR........
     hPPARbeta  ASCGSLNMEC RVCGDKASGF HYGVHACEGC KGFFRRTIRM KLEYE...KC ER........
    hPPARgamma  PSNSLMAIEC RVCGDKASGF HYGVHACEGC KGFFRRTIRL KLIYD...RC DL........
          hVDR  AVLTLPTATV ATLPGLAAAS PAGGLLKLPF AGLQAATVLN SVQTQLQAPA QAVLQPQMSA
           hER  KET....RYC AVCNDYASGY HYGVWSCEGC KAFFKRSIQG HN..DYMCPA TN........
           hGR  ATTGPPPKLC LVCSDEASGC HYGVLTCGSC KVFFKRAVEG QHNYLCAGRN D.........
           hPR  SFESLPQKIC LICGDEASGC HYGVLTCGSC KVFFKRAMEG QHNYLCAGRN D.........
           hMR  TGSSRPSKIC LVCGDEASGC HYGVVTCGSC KVFFKRAVEG QHNYLCAGRN D.........
           hAR  .....PQKTC LICGDKASGC HYGALTCGSC KVFFKRAAEG KQKYLCASRN D.........
```

FIG.3K

```
          661                                                                720
rTRalpha  .CCVIDKITR NQCQLCRFKK CIAVGMAMDL VLDDSKRVAK RKLIEQNRER RRK..EEMIR
hTRalpha  .CCVIDKITR NQCQLCRFKK CIAVGMAMDL VLDDSKRVAK RKLIEQNRER RRK..EEMIR
 hTRbeta  .KCVIDKVTR NQCQECRFKK CIYVGMATDL VLDDSKRLAK RKLIEENREK RRR..EELQK
hRARalpha .NCIINKVTR NRCQYCRLQK CFEVGMSKES VRND...... .......RNK KKK..EVPKP
hRARgamma .NCIINKVTR NRCQYCRLQK CFEVGMSKEA VRND...... .......RNK KKK..EVKEE
hRXRalpha .DCLIDKRQR NRCQYCRYQK CLAMGMKREA VQEERQRG.. ....KDRNEN EVE..STSSA
 hRXRbeta .DCTVDKRQR NRCQYCRYQK CLATGMKREA VQEERQRG.. ....KDK.DG DGE..CAGGA
hPPARalpha .SCKIQKKNR NKCQYCRFHK CLSVGMSHNA IRFG...... .RMPRSEKAK LKA..EILTC
 hPPARbeta .SCKIQKKNR NKCQYCRFQK CLALGMSHNA IRFG...... .RMPEAEKRK LVA..GLTAN
hPPARgamma .NCRIHKKSR NKCQYCRFQK CLAVGMSHNA IRFG...... .RMPQAEKEK LLA..EI.SS
      hVDR LQAMQQTQTT AATTASIVQK ASEPSVSVAT LQTAGLSINP AIISAASLGA QPQFISSLTT
       hER .QCTIDKNRR KSCQACRLRK CYEVGMMKGG IRKDRRGGRM LKHKRQRDDG EGR..GEVGS
       hGR ..CIIDKIRR KNCPACRYRK CLQAGMNLEA .......... RKTKK..KIK GIQ..QATT.
       hPR ..CIVDKIRR KNCPACRLRK CCQAGMVLGG .......... RKFKKFNKVR VVR..ALDAV
       hMR ..CIIDKIRR KNCPACRLQK CLQAGMNLGA .......... RKSKKLGKLK GIH..EEQPQ
       hAR ..CTIDKFRR KNCPSCRLRK CYEAGMTLGA .......... RKLKKLGNLK LQE..EGEAS
```

FIG.3L

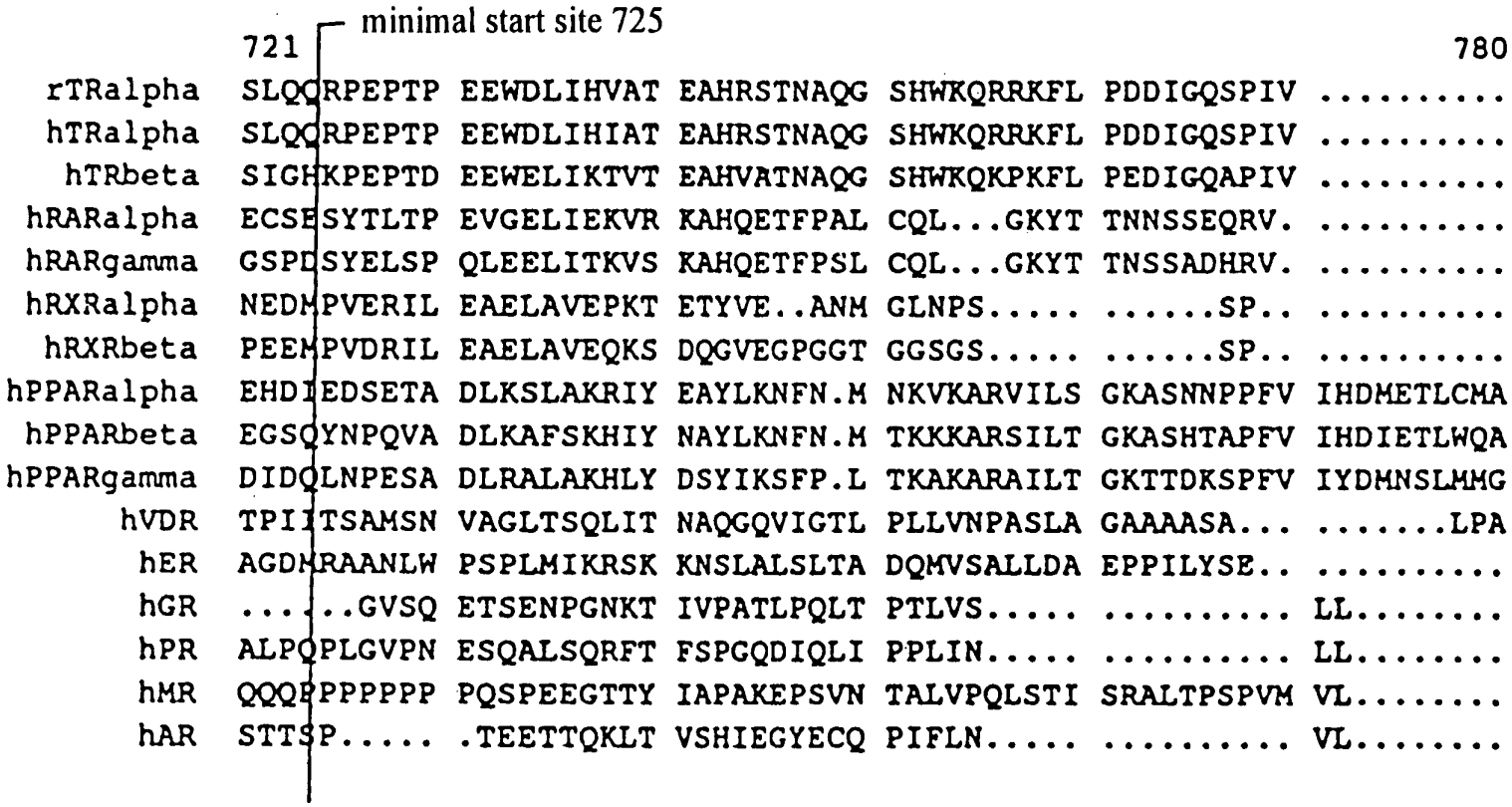

minimal start site 725
721
780
rTRalpha SLQQRPEPTP EEWDLIHVAT EAHRSTNAQG SHWKQRRKFL PDDIGQSPIV .....
hTRalpha SLQQRPEPTP EEWDLIHIAT EAHRSTNAQG SHWKQRRKFL PDDIGQSPIV .....
hTRbeta SIGHKPEPTD EEWELIKTVT EAHVATNAQG SHWKQKPKFL PEDIGQAPIV .....
hRARalpha ECSESYTLTP EVGELIEKVR KAHQETFPAL CQL...GKYT TNNSSEQRV. .....
hRARgamma GSPDSYELSP QLEELITKVS KAHQETFPSL CQL...GKYT TNSSADHRV. .....
hRXRalpha NEDMPVERIL EAELAVEPKT ETYVE..ANM GLNPS..... ......SP.. .....
hRXRbeta PEEMPVDRIL EAELAVEQKS DQGVEGPGGT GGSGS..... ......SP.. .....
hPPARalpha EHDIEDSETA DLKSLAKRIY EAYLKNFN.M NKVKARVILS GKASNNPPFV IHDMETLCMA
hPPARbeta EGSQYNPQVA DLKAFSKHIY NAYLKNFN.M TKKKARSILT GKASHTAPFV IHDIETLWQA
hPPARgamma DIDQLNPESA DLRALAKHLY DSYIKSFP.L TKAKARAILT GKTTDKSPFV IYDMNSLMMG
hVDR TPIITSAMSN VAGLTSQLIT NAQGQVIGTL PLLVNPASLA GAAAASA... ....LPA
hER AGDMRAANLW PSPLMIKRSK KNSLALSLTA DQMVSALLDA EPPILYSE.. .....
hGR .....GVSQ ETSENPGNKT IVPATLPQLT PTLVS..... ..... LL.....
hPR ALPQPLGVPN ESQALSQRFT FSPGQDIQLI PPLIN..... ..... LL.....
hMR QQQPPPPPPP PQSPEEGTTY IAPAKEPSVN TALVPQLSTI SRALTPSPVM VL.....
hAR STTSP..... .TEETTQKLT VSHIEGYECQ PIFLN..... ..... VL.....

FIG.3M

```
            781                                                        840
  rTRalpha  .......... .SMPDGDKVD LEAFSEFTKI ITPAITRVVD FAKKLPMFSE LPCEDQIILL
  hTRalpha  .......... .SMPDGDKVD LEAFSEFTKI ITPAITRVVD FAKKLPMFSE LPCEDQIILL
   hTRbeta  .......... .NAPEGGKVD LEAFSHFTKI ITPAITRVVD FAKKLPMFCE LPCEDQIILL
 hRARalpha  .......... .......SLD IDLWDKFSEL STKCIIKTVE FAKQLPGFTT LTIADQITLL
 hRARgamma  .......... .......QLD LGLWDKFSEL ATKCIIKIVE FAKRLPGFTG LSIADQITLL
 hRXRalpha  .......... .NDPVTNICQ A.......... ADKQLFTLVE WAKRIPHFSE LPLDDQVILL
  hRXRbeta  .......... .NDPVTNICQ A......... ADKQLFTLVE WAKRIPHFSS LPLDDQVILL
hPPARalpha  EKTLVAKLVA NGIQN.KEVE VRIFHCCQCT SVETVTELTE FAKAIPAFAN LDLNDQVTLL
 hPPARbeta  EKGLVWKQLV NGLPPYKEIS VHVFYRCQCT TVETVRELTE FAKSIPSFSS LFLNDQVTLL
hPPARgamma  EDKIKFKHIT PLQEQSKEVA IRIFQGCQFR SVEAVQEITE YAKNIPGFIN LDLNDQVTLL
       hVDR  QGLQVQTVAP QLLLNSQGQI IATIGNGPTA AIPSTASVLP KATVPLTLTK TTTQGPVGKV
        hER  .......... .YDPTRPFSE ASMMGLLTNL ADRELVHMIN WAKRVPGFVD LTLHDQVHLL
        hGR  EVIEPEVLYA GYDSSVPDST WRIMTTLNML GGRQVIAAVK WAKAIPGFRN LHLDDQMTLL
        hPR  MSIEPDVIYA GHDNTKPDTS SSLLTSLNQL GERQLLSVVK WSKSLPGFRN LHIDDQITLI
        hMR  ENIEPEIVYA GYDSSKPDTA ENLLSTLNRL AGKQMIQVVK WAKVLPGFKN LPLEDQITLI
        hAR  EAIEPGVVCA GHDNNQPDSF AALLSSLNEL GERQLVHVVK WAKALPGFRN LHVDDQMAVI
```

FIG.3N

```
            841                                                        900
  rTRalpha  KGCCMEIMSL RAAVRY..DP ESDTLTLSGE MTVKRKQLK. ..N..GGLGV VSDAIFELGK
  hTRalpha  KGCCMEIMSL RAAVRY..DP ESDTLTLSGE MAVKREQLK. ..N..GGLGV VSDAIFELGK
   hTRbeta  KGCCMEIMSL RAAVRY..DP ESETLTLNGE MAVIRGQLK. ..N..GGLGV VSDAIFDLGM
 hRARalpha  KAACLDILIL RICTRY..TP EQDTMTFSDG LTLNRTQMH. ..N..AGFGP LTDLVFAFAN
 hRARgamma  KAACLDILML RICTRY..TP EQDTMTFSDG LTLNRTQMH. ..N..AGFGP LTDLVFAFAG
 hRXRalpha  RAGWNELLIA SFSHRS..IA VKDGILLATG LHVHRNSAH. ..S.AGVGAI FDRVLTELVS
  hRXRbeta  RAGWNELLIA SFSHRS..ID VRDGILLATG LHVHRNSAH. ..S.AGVGAI FDRVLTELVS
hPPARalpha  KYGVYEAIFA MLSSVM..NK DGMLVAYGNG F.ITREFLK. ..SLRKPFCD IMEPKFDFAM
 hPPARbeta  KYGVHEAIFA MLASIV..NK DGLLVANGSG F.VTREFLR. ..SLRKPFSD IIEPKFEFAV
hPPARgamma  KYGVHEIIYT MLASLM..NK DGVLISEGQG F.MTREFLK. ..SLRKPFGD FMEPKFEFAV
       hVDR APSKVIIAPQ PSVVKPVTSL TAAGVIACGE MPTVGQLVNK PSAVKDEEAI NLEEIREFAK
        hER ECAWLEILMI GLVWRS..ME HPGKLLFAPN LLLDRNQGK. ..CVEGMVEI FDMLLAT.SS
        hGR QYSWMFLMAF ALGWRSYRQS SANLLCFAPD LIINEQRMT. ....LPCMYD QCKHMLYVSS
        hPR QYSWMSLMVF GLGWRSYKHV SGQMLYFAPD LILNEQRMK. ....ESSFYS LCLTMWQIPQ
        hMR QYSWMCLSSF ALSWRSYKHT NSQFLYFAPD LVFNEEKMH. ....QSAMYE LCQGMHQISL
        hAR QYSWMGLMVF AMGWRSFTNV NSRMLYFAPD LVFNEYRMH. ....KSRMYS QCVRMRHLSQ
```

FIG.30

```
            901                                                        960
  rTRalpha  SLSAFNLDDT EVALLQAVLL MSTD..... ..RSGLLCVD KIEKSQEAYL LA...FEHYV
  hTRalpha  SLSAFNLDDT EVALLQAVLL MSTD..... ..RSGLLCVD KIEKSQEAYL LA...FEHYV
   hTRbeta  SLSSFNLDDT EVALLQAVLL MSSD..... ..RPGLACVE RIEKYQDSFL LA...FEHYI
 hRARalpha  QLLPLEMDDA ETGILSAICL ICGD..... ..RQDLEQPD RVDMLQEPLL EA...LKVYV
 hRARgamma  QLLPLEMDDT ETGLLSAICL ICGD..... ..RMDLEEPE KVDKLQEPLL EA...LRLYA
 hRXRalpha  KMRDMQMDKT ELGCLRAIVL FNPDS..... ...KGLSNPA EVEALREKVY AS...LEAYC
  hRXRbeta  KMRDMRMDKT ELGCLRAIIL FNPDA..... ...KGLSNPS EVEVLREKVY AS...LETYC
hPPARalpha  KFNALELDDS DISLFVAAII CCGD..... ..RPGLLNVG HIEKMQEGIV HV...LRLHL
 hPPARbeta  KFNALELDDS DLALFIAAII LCGD..... ..RPGLMNVP RVEAIQDTIL RA...LEFHL
hPPARgamma  KFNALELDDS DLAIFIAVII LSGD..... ..RPGLLNVK PIEDIQDNLL QA...LELQL
       hVDR NFKIRRLSLG LTQTQVGQAL TATEGPAYSQ SAICRFEKLD ITPKSAQKLK PVLERWLAEA
        hER RFRMMNLQGE EFVCLKSIIL LNSGVYTFLS STLKSLEEKD HIHRVLDKIT DTLIHLMAKA
        hGR ELHRLQVSYE EYLCMKTLLL LSS....... VPKDGLKSQE LFDEIRMTYI KELGKAIVKR
        hPR EFVKLQVSQE EFLCMKVLLL LNT....... IPLEGLRSQT QFEEMRSSYI RELIKAIGLR
        hMR QFVRLQLTFE EYTIMKVLLL LST....... IPKDGLKSQA AFEEMRTNYI KELRKMVTKC
        hAR EFGWLQITPQ EFLCMKALLL FSI....... IPVDGLKNQK FFDELRMNYI KELDRIIACK
```

FIG.3P

```
            961                                                        1020
  rTRalpha  NHRKHNIPHF WPKLL....M KVTDLRMIGA CHASRFL..H MKVEC..PTE LFPPLFLEVF
  hTRalpha  NHRKHNIPHF WPKLL....M KVTDLRMIGA CHASRFL..H MKVEC..PTE LFPPLFLEVF
   hTRbeta  NYRKHHVTHF WPKLL....M KVTDLRMIGA CHASRFL..H MKVEC..PTE LLPPLFLEVF
 hRARalpha  RKRRPSRPHM FPKML....M KITDLRSISA KGAERVI..T LKMEI..PGS M.PPLIQEML
 hRARgamma  RRRRPSQPYM FPRML....M KITDLRGIST KGAERAI..T LKMEI..PGP M.PPLIREML
 hRXRalpha  KHKYPEQPGR FAKLL....L RLPALRSIGL KCLEHLF..F FKL.I..GDT PIDTFLMEML
  hRXRbeta  KQKYPEQQGR FAKLL....L RLPALRSIGL KCLEHLF..F FKL.I..GDT PIDTFLMEML
hPPARalpha  QSNHPDDIFL FPKLL....Q KMADLRQLVT EHAQLVQ..I IKKTE..SDA ALHPLLQEIY
 hPPARbeta  QANHPDAQYL FPKLL....Q KMADLRQLVT EHAQMMQ..R IKKTE..TET SLHPLLQEIY
hPPARgamma  KLNHPESSQL FAKVL....Q KMTDLRQIVT EHVQLLH..V IKKTE..TDM SLHPLLQEIY
       hVDR ELWNQKGQQN LMEFVGGEPS KKRKRRTSFT PQAIEVLNTY FEKNSLPTGQ EITEIAKELN
        hER GLTLQQQHQR LAQLL....L ILSHIRHMSN KGMEHLY..S MKC.K..NVV PLYDLLLEML
        hGR EGNSSQNWQR FYQLT....K LLDSMHEVVE NLLNYCFQTF LD.KT..MSI EFPEMLAEII
        hPR QKGVVSSSQR FYQLT....K LLDNLHDLVK QLHLYCLNTF IQSRA..LSV EFPEMMSEVI
        hMR PNNSGQSWQR FYQLT....K LLDSMHDLVS DLLEFCFYTF RESHA..LKV EFPAMLVEII
        hAR RKNPTSCSRR FYQLT....K LLDSVQPIAR ELHQFTFDLL IKSHM..VSV DFPEMMAEII
```

FIG.3Q

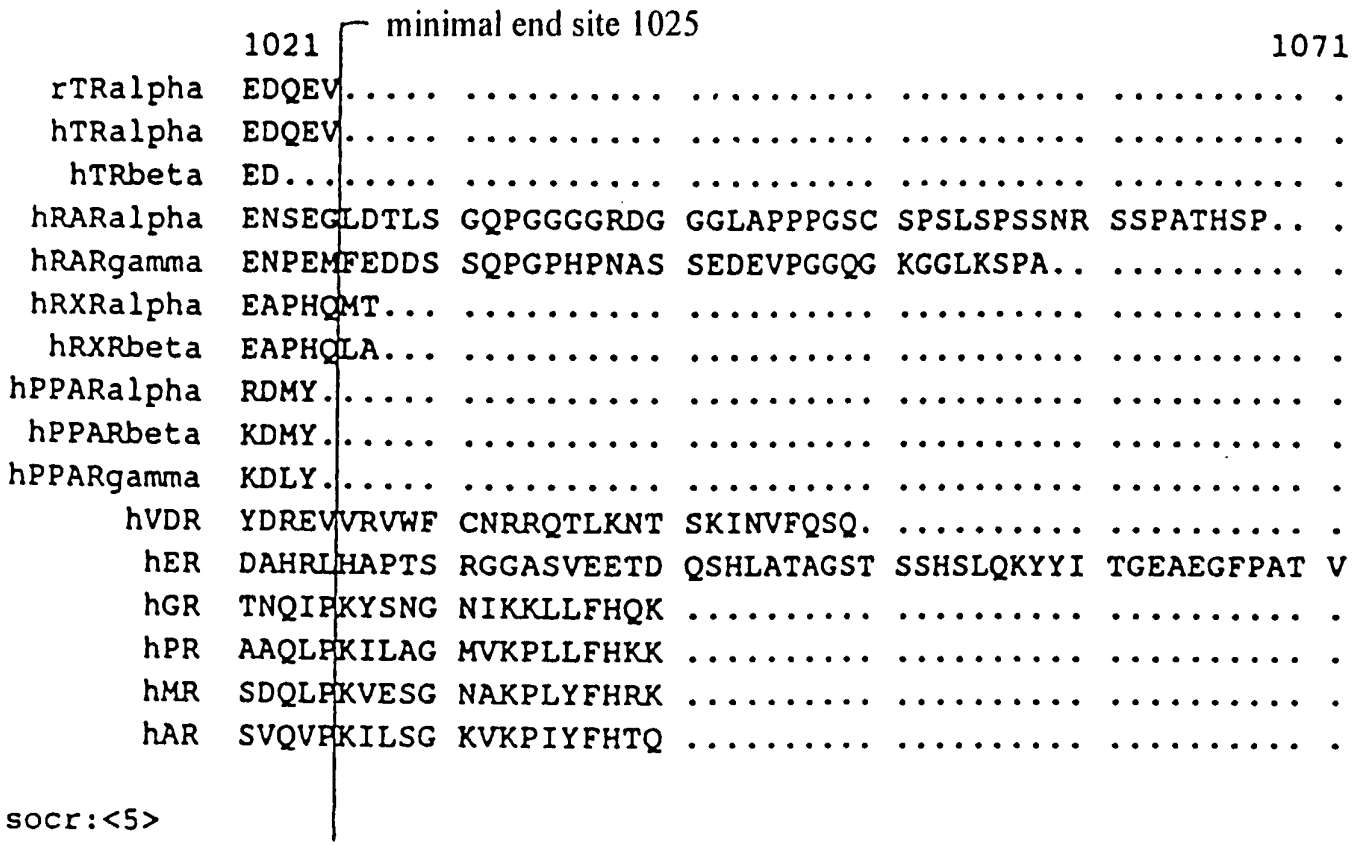

minimal end site 1025
1021
1071
rTRalpha EDQEV..... ....
hTRalpha EDQEV..... ....
hTRbeta ED..... ....
hRARalpha ENSEGLDTLS GQPGGGGRDG GGLAPPPGSC SPSLSPSSNR SSPATHSP.. .
hRARgamma ENPEMFEDDS SQPGPHPNAS SEDEVPGGQG KGGLKSPA.. ..... .
hRXRalpha EAPHQMT... ....
hRXRbeta EAPHQLA... ....
hPPARalpha RDMY..... ....
hPPARbeta KDMY..... ....
hPPARgamma KDLY..... ....
hVDR YDREVVRVWF CNRRQTLKNT SKINVFQSQ. ....
hER DAHRLHAPTS RGGASVEETD QSHLATAGST SSHSLQKYYI TGEAEGFPAT V
hGR TNQIPKYSNG NIKKLLFHQK ....
hPR AAQLPKILAG MVKPLLFHKK ....
hMR SDQLPKVESG NAKPLYFHRK ....
hAR SVQVPKILSG KVKPIYFHTQ ....
socr:<5>

FIG.3R

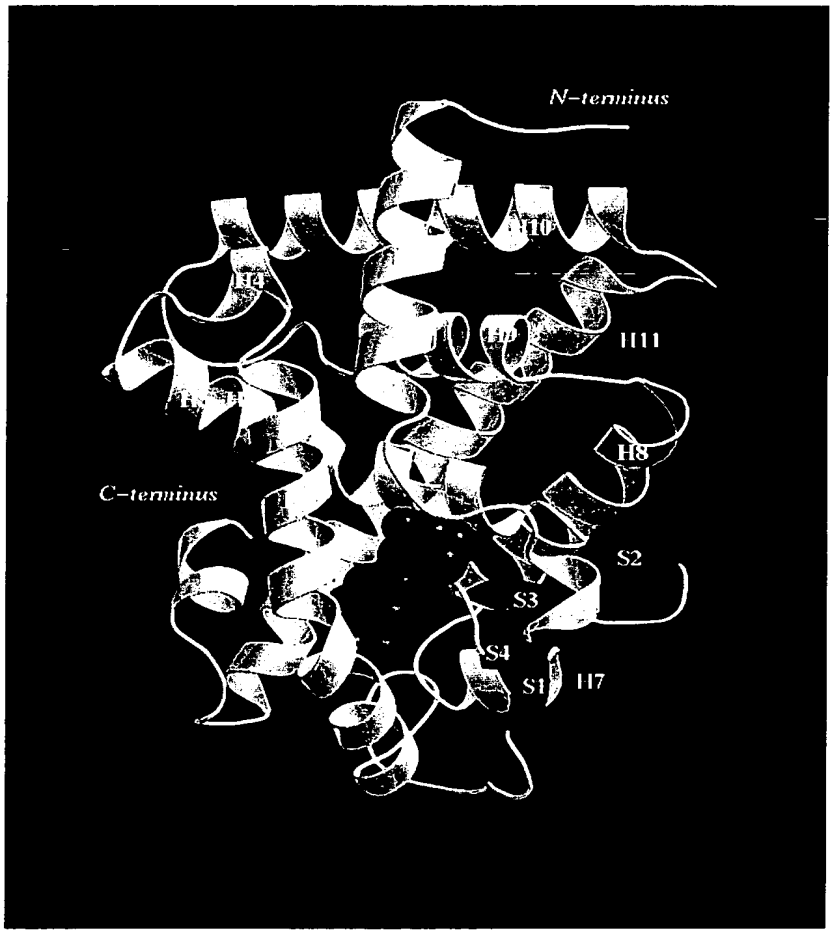
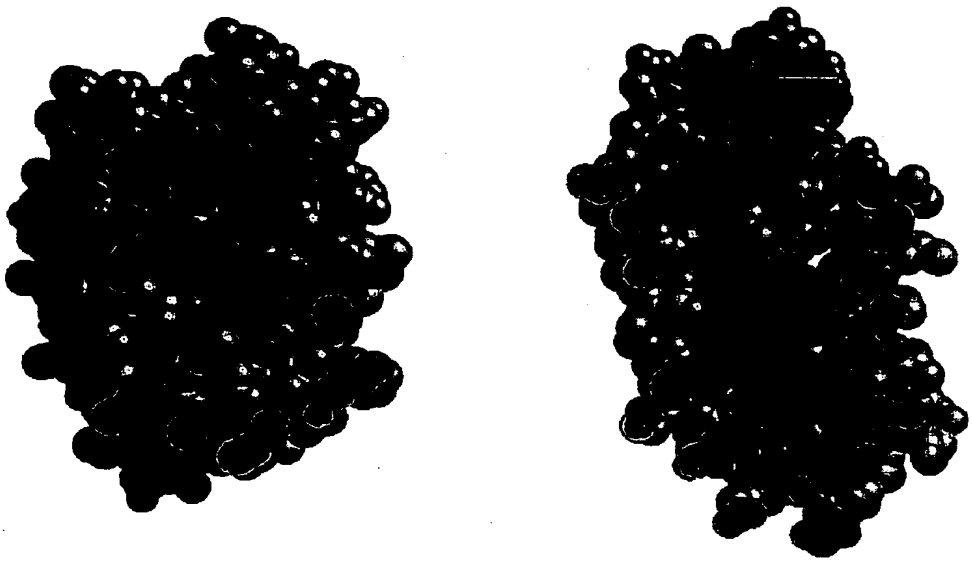


FIG. 4

FIG. 5



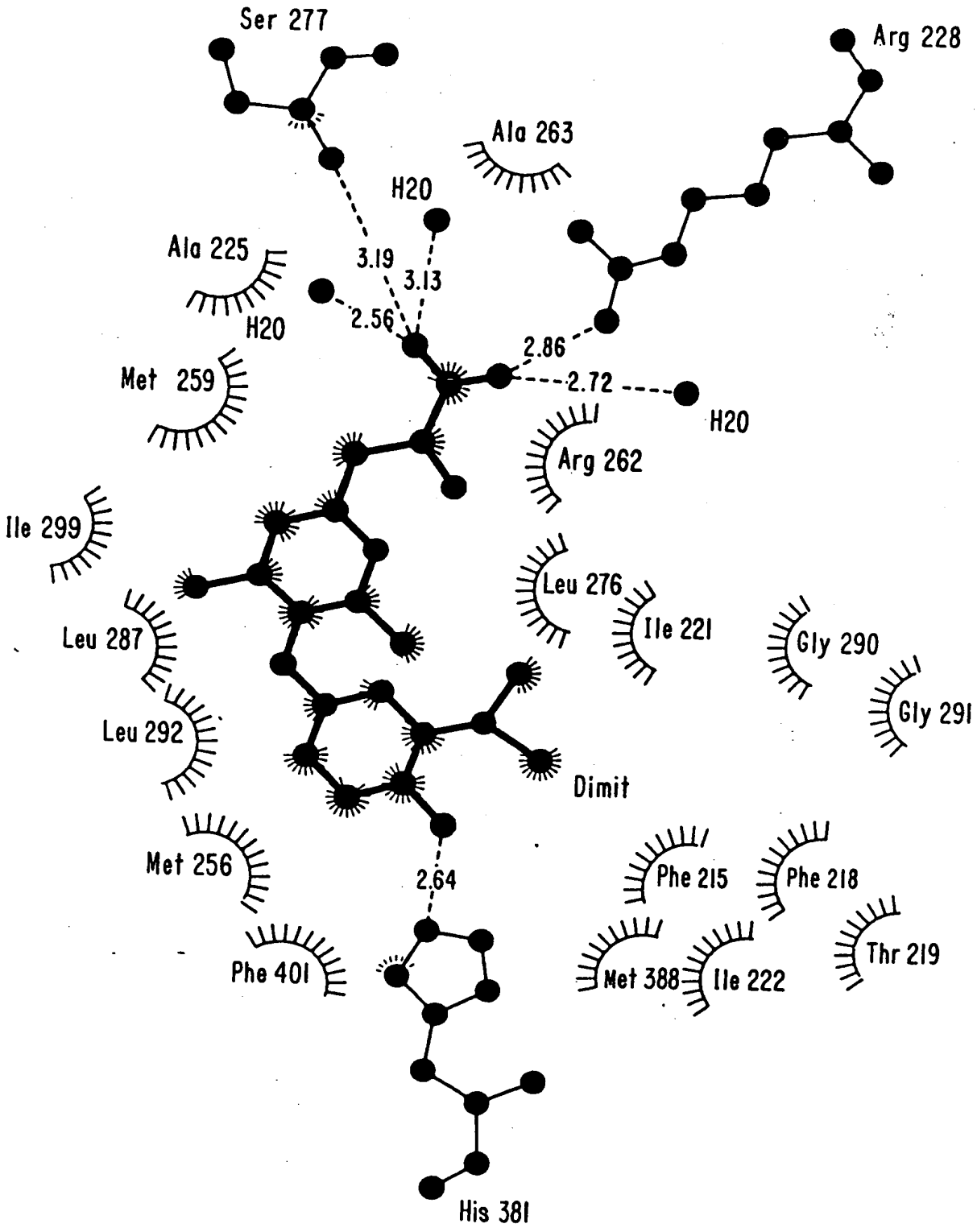

Ser 277
Arg 228
Ala 263
H20
Ala 225
3.19
3.13
H20
2.56
2.86
Met 259
2.72
H20
Arg 262
Ile 299
Leu 276
Ile 221
Leu 287
Gly 290
Gly 291
Leu 292
Dimit
Met 256
2.64
Phe 215
Phe 218
Thr 219
Phe 401
Met 388
Ile 222
His 381

FIG.6

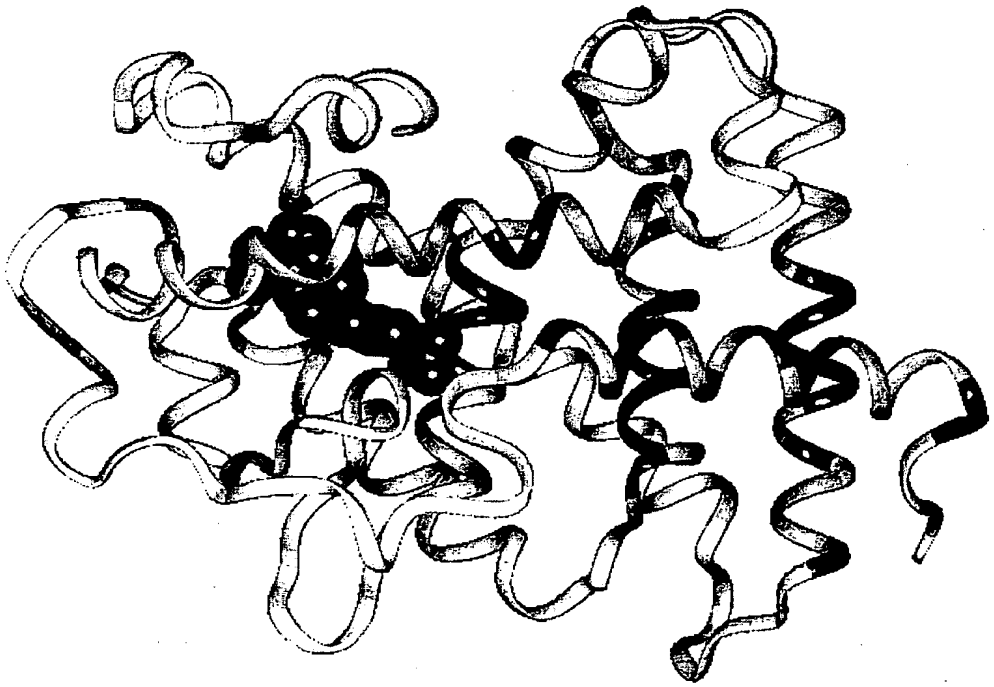


FIG. 7

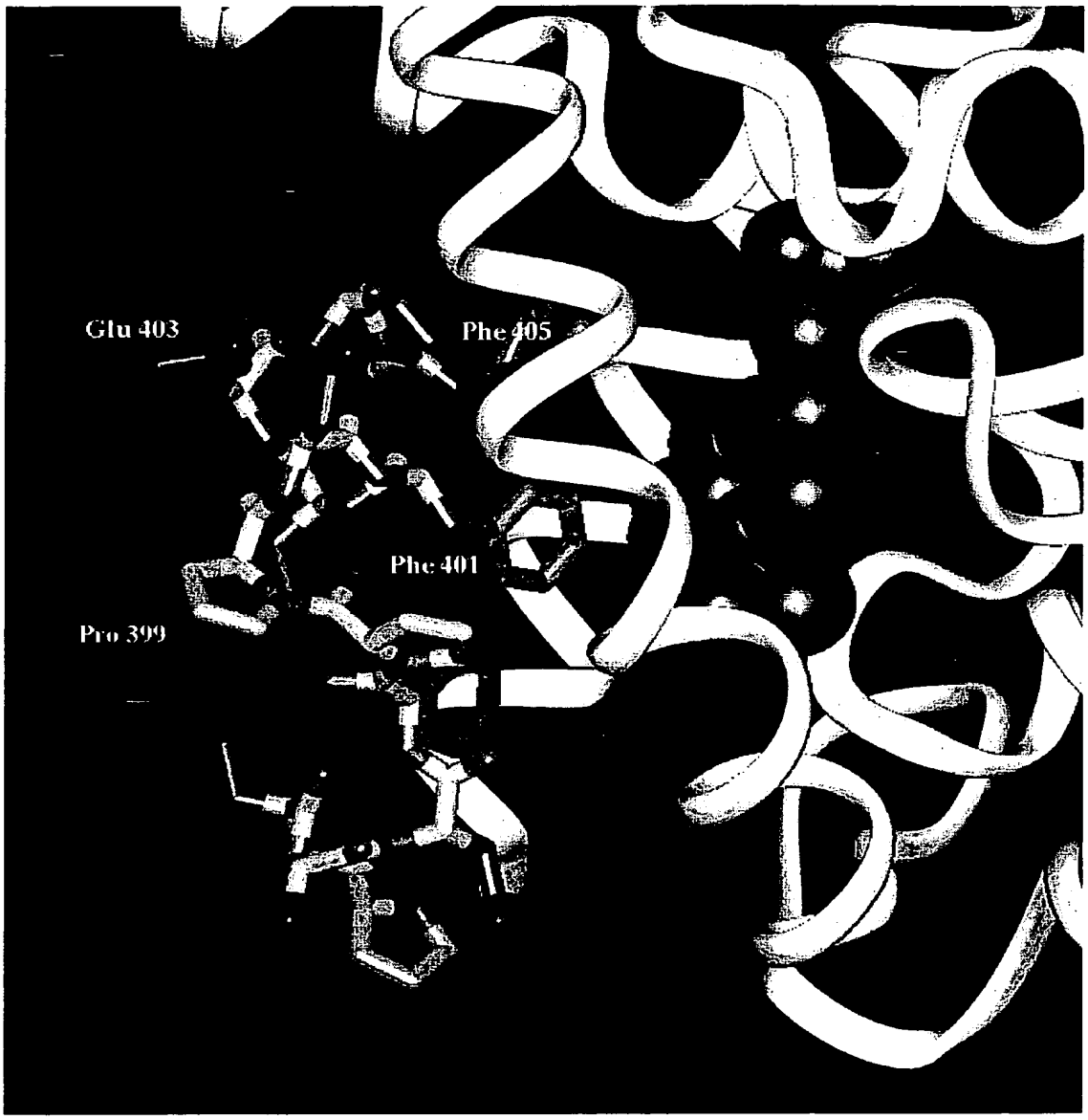


FIG. 8

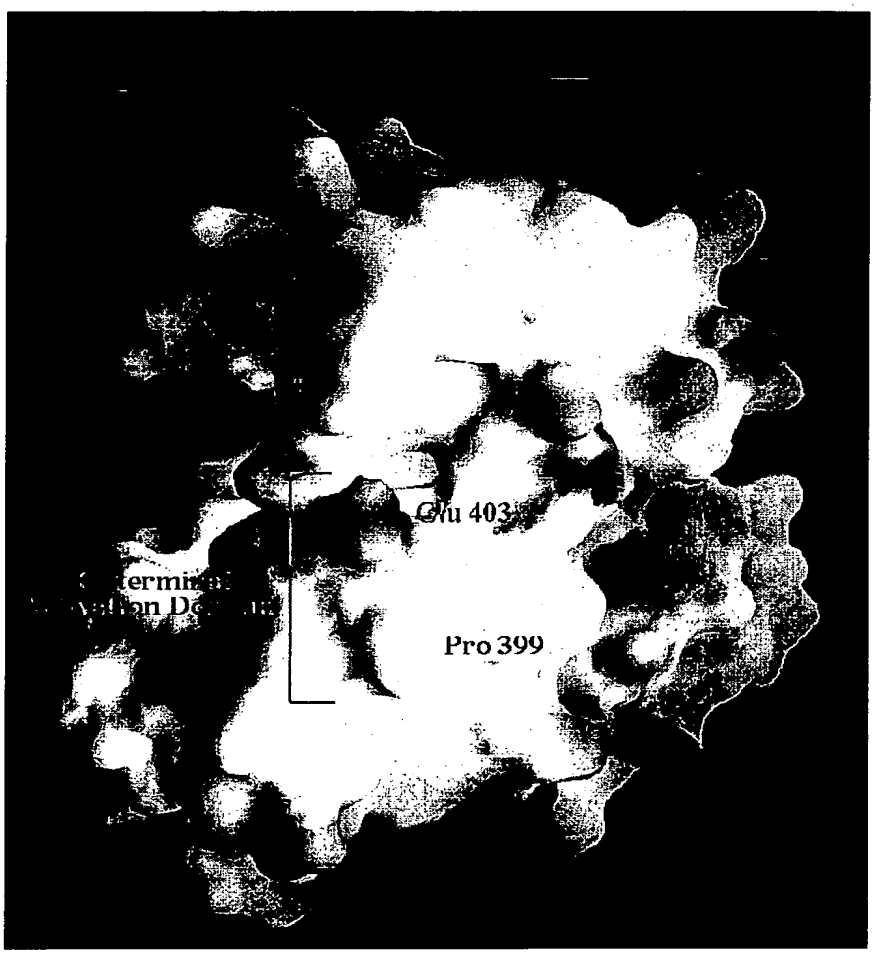
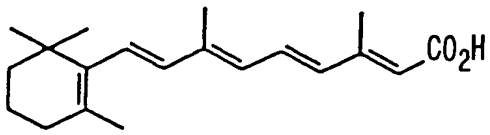
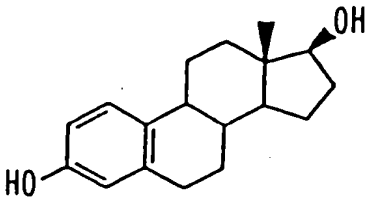


FIG. 9

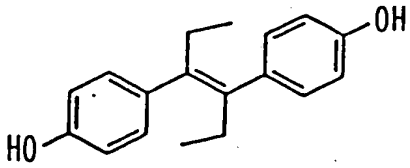
AGONISTS



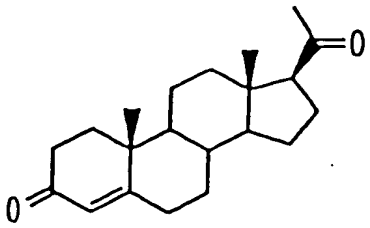
Retinoic Acid



Estradiol

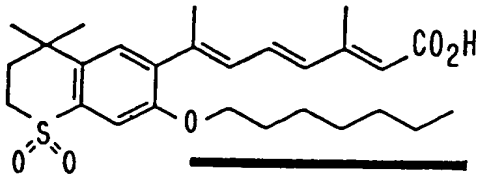


Diethylstilbestrol

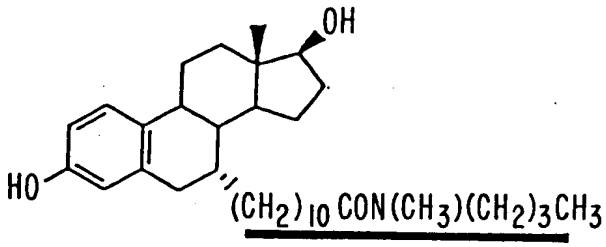


Progesterone

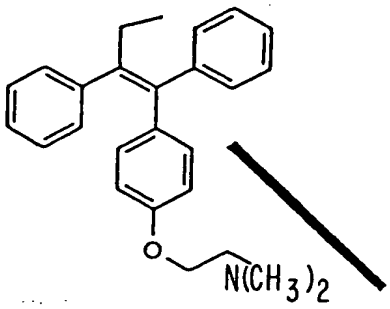
ANTAGONISTS



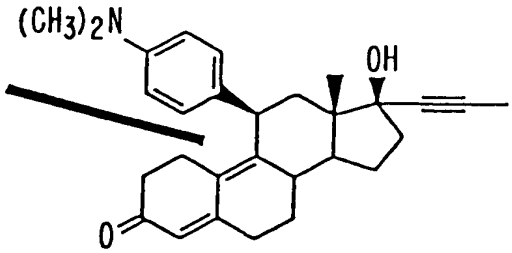
RO 46-8515



ICI 164384



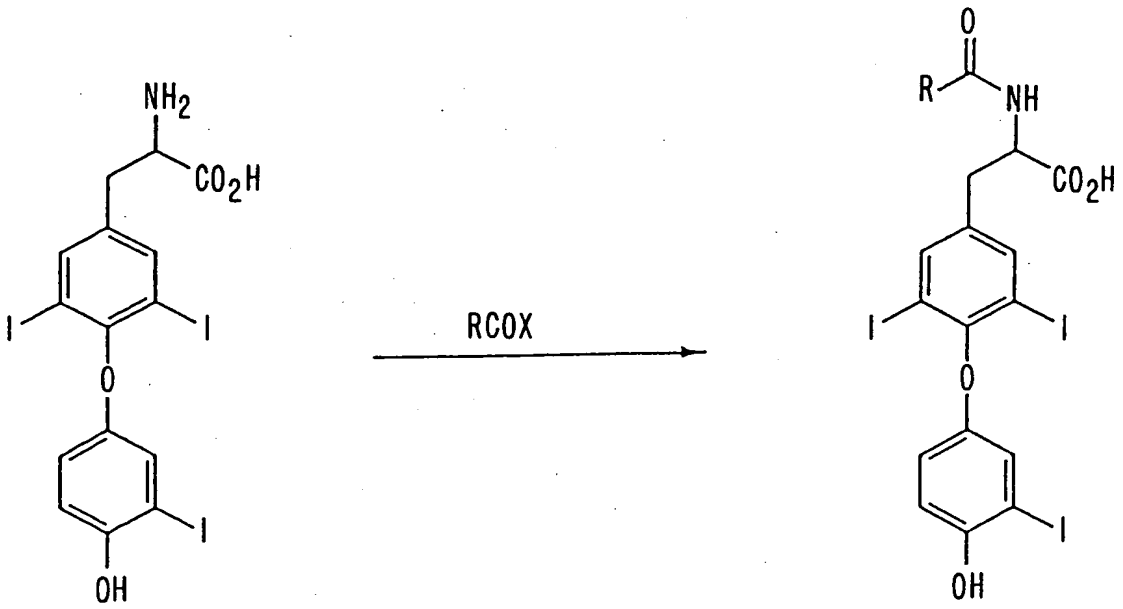
Tamoxifen



RU 486

FIG. 10

shows position of extension group



Compound	RCOX
TS1	Ph_2CHCO_2NHS
TS2	$C_{16}H_{33}CO_2NHS$
TS3	FMOC-Cl
TS4	$tBOC_2O$
TS5	$tBOC_2O$

FIG. 11

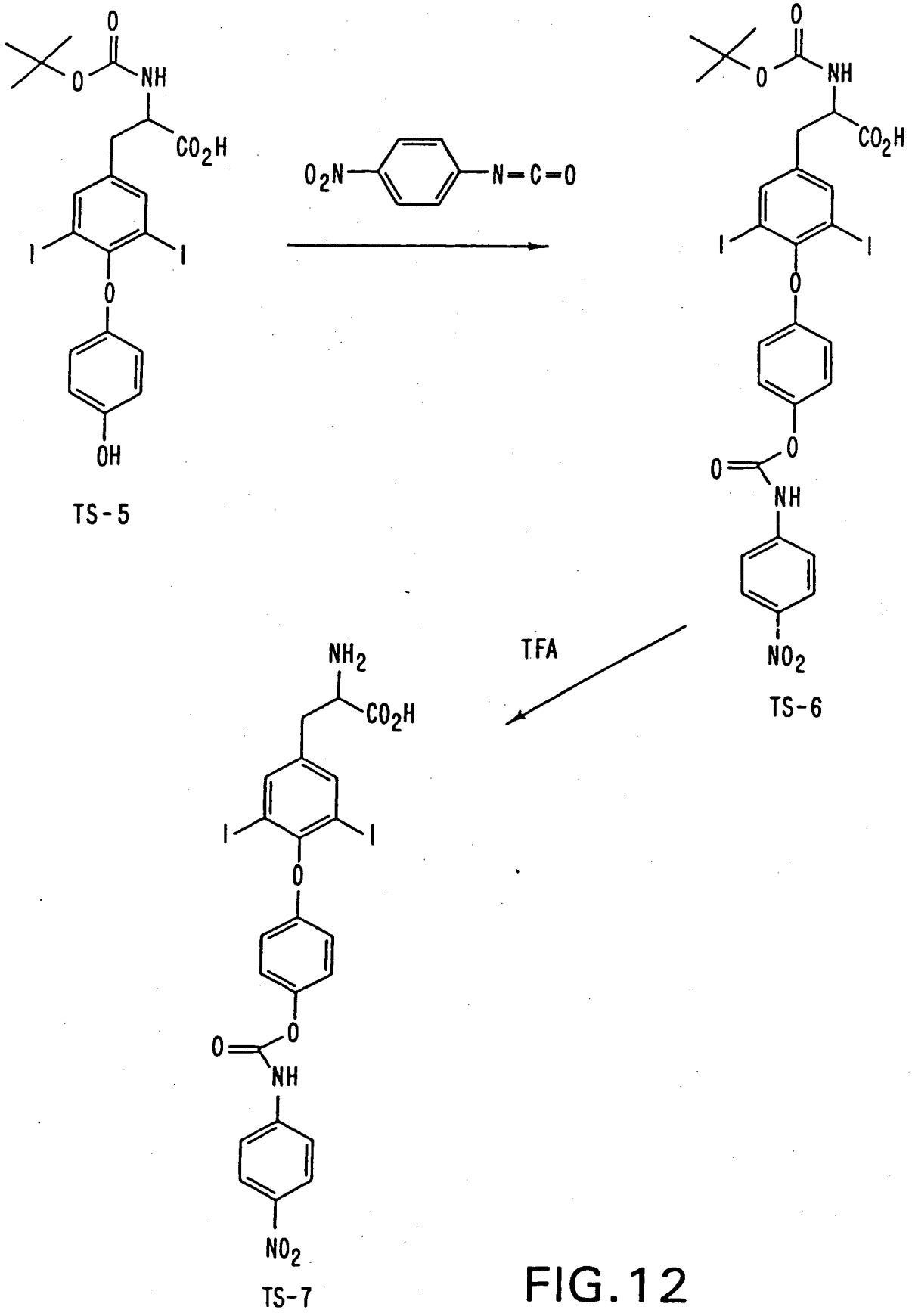
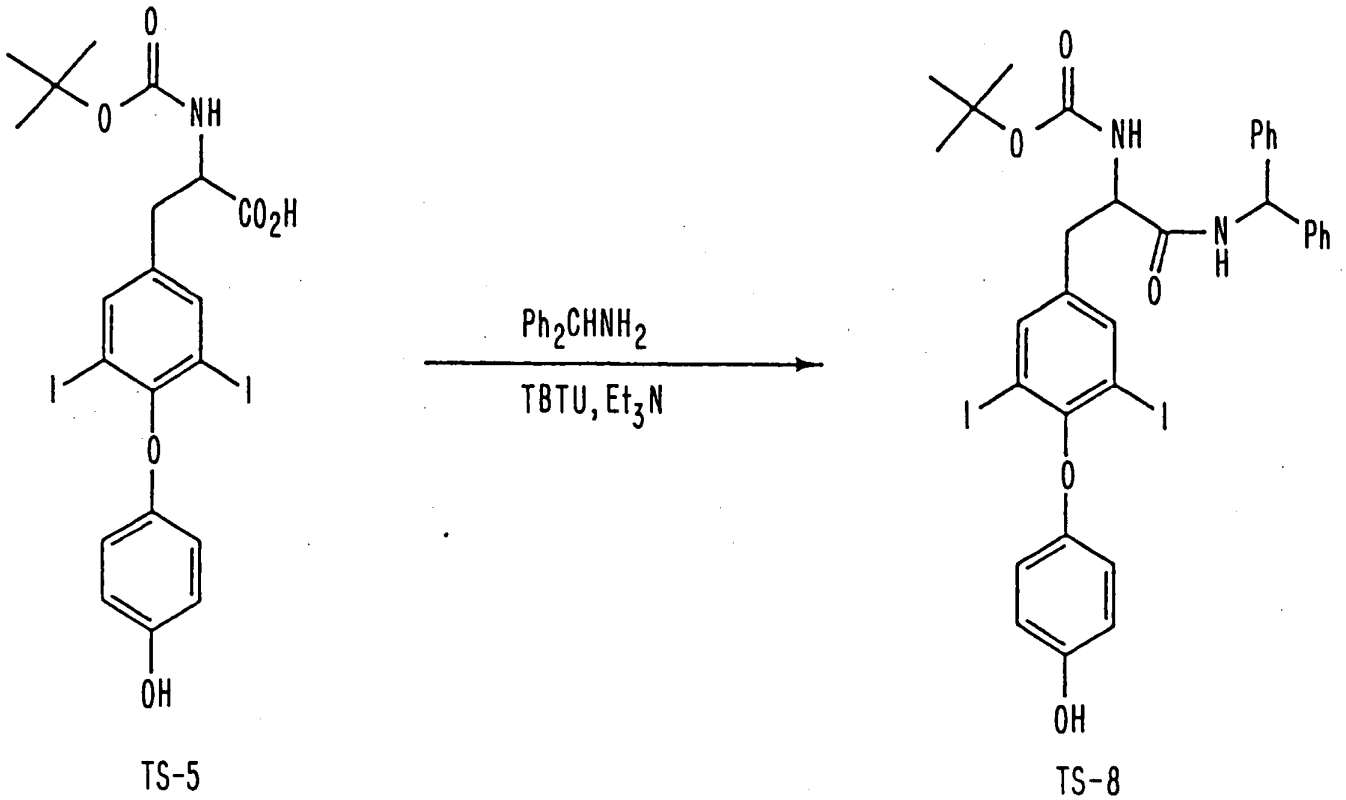


FIG. 12



TS-5

TS-8

FIG.13

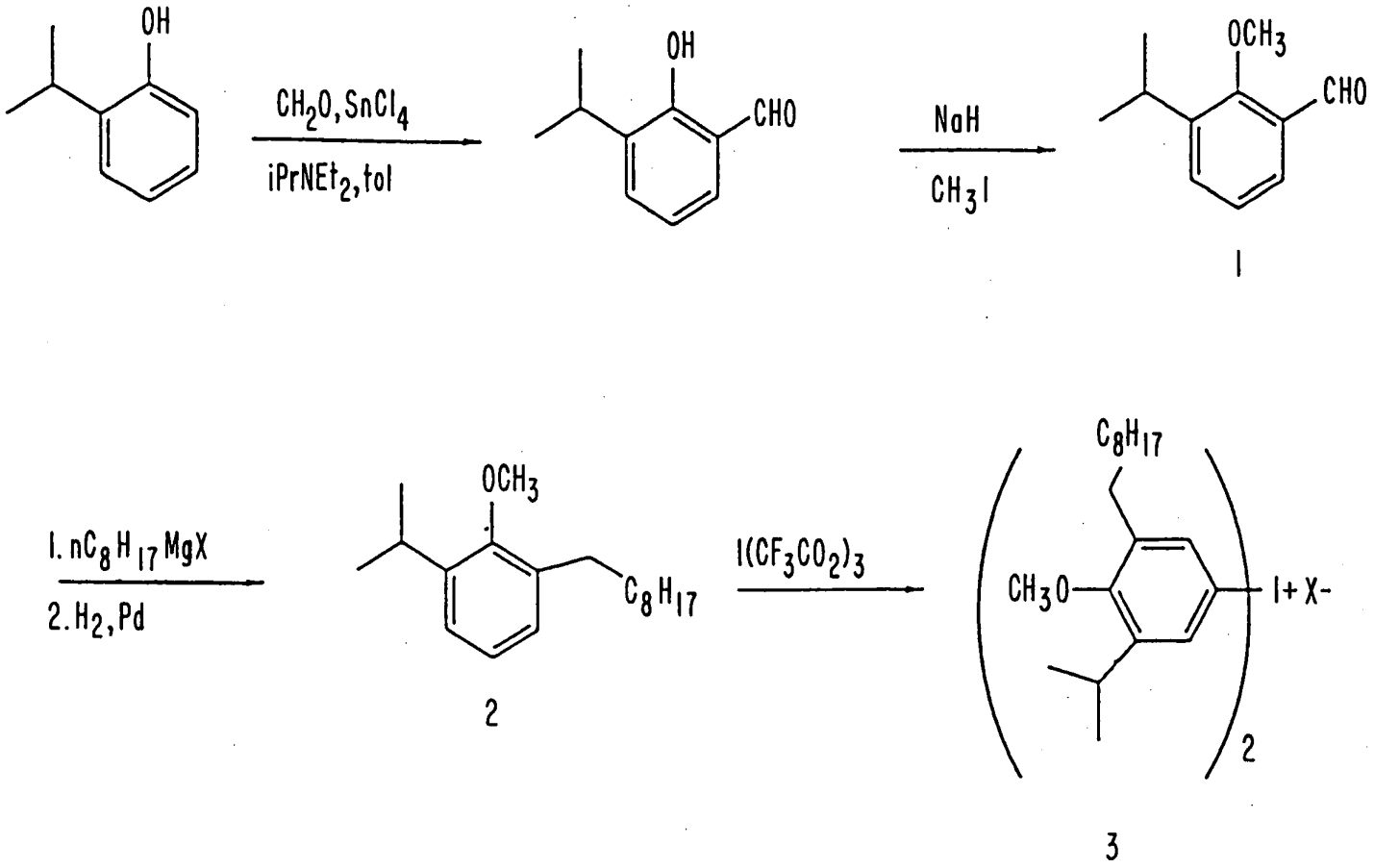

OH
$CH_2O, SnCl_4$
$iPrNEt_2$, tol
OH
CHO
NaH
CH_3I
OCH_3
CHO
1
1. $nC_8H_{17}MgX$
2. H_2, Pd
OCH_3
C_8H_{17}
2
$I(CF_3CO_2)_3$
C_8H_{17}
CH_3O
$I^+ X^-$
2
3

FIG. 14A

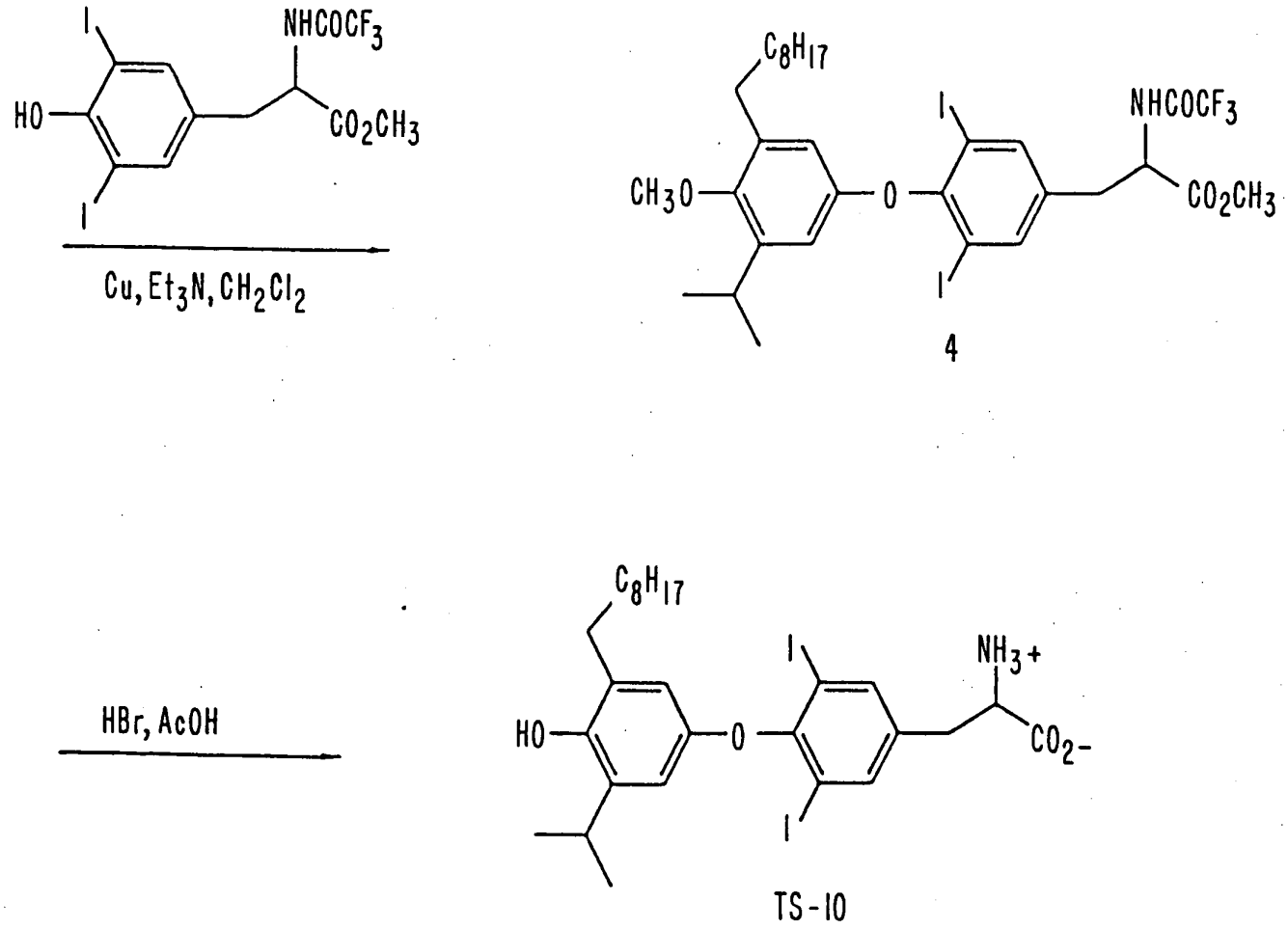
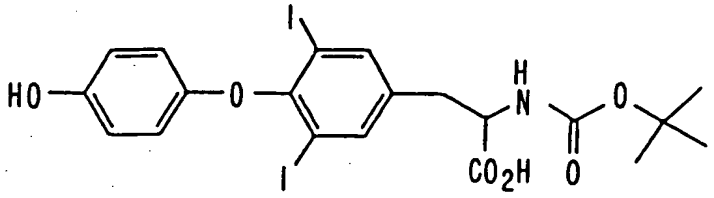
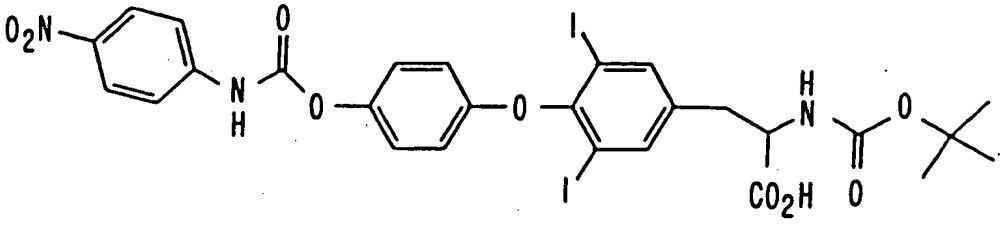

I
NHCOCF3
HO
CO2CH3
I
Cu, Et3N, CH2Cl2
C8H17
I
NHCOCF3
CH3O
O
CO2CH3
I
4
HBr, AcOH
C8H17
I
NH3+
HO
O
CO2-
I
TS-10

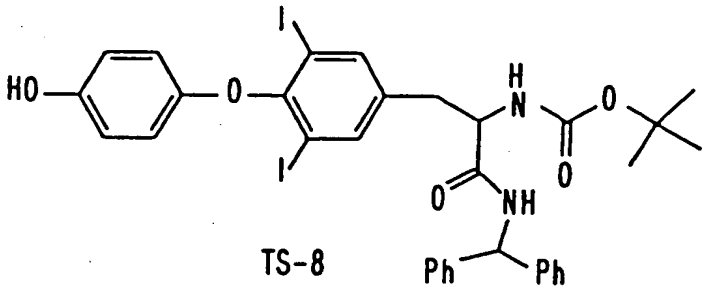
FIG.14B



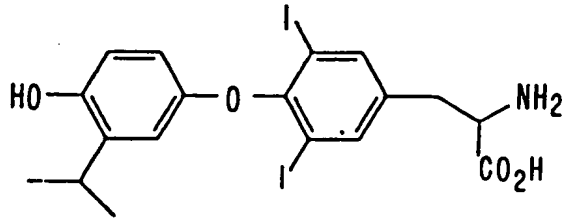
TS-5



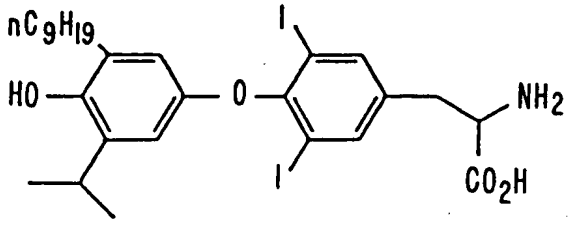
TS-6



TS-8



TS-9



TS-10

FIG.15

FIG.16

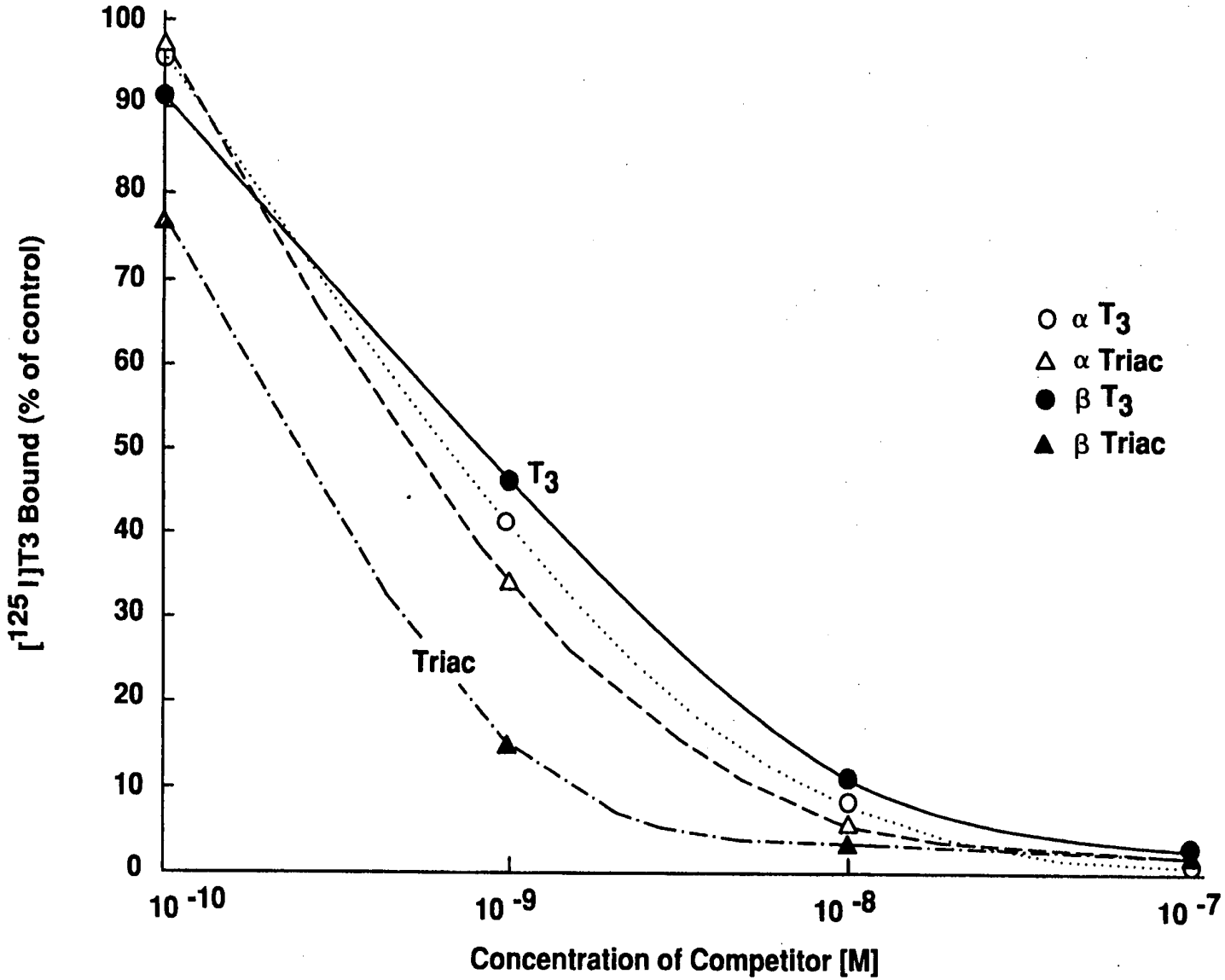

100
90
80
70
60
50
40
30
20
10
0
[125I]T3 Bound (% of control)
T3
Triac
10 -10
10 -9
10 -8
10 -7
Concentration of Competitor [M]
α T3
α Triac
β T3
β Triac

FIG.17A

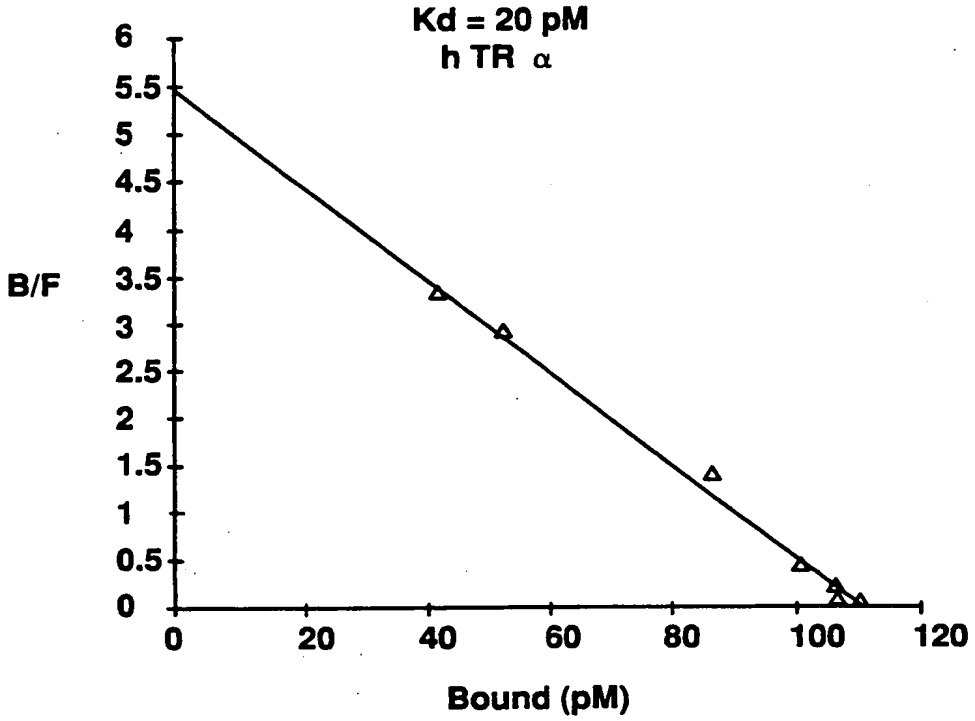


FIG.17B

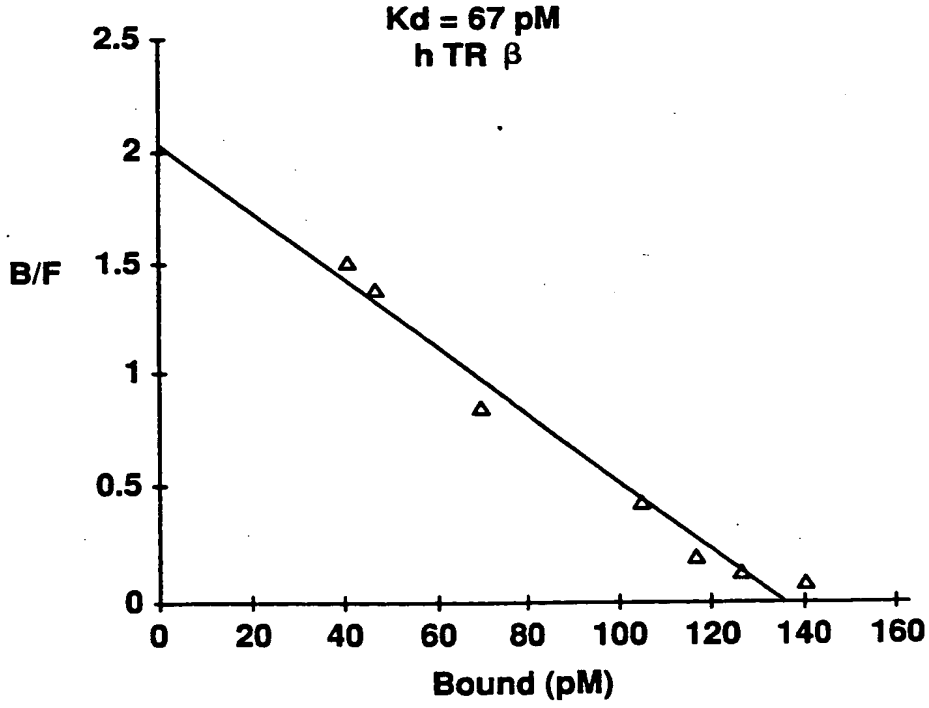


FIG.18

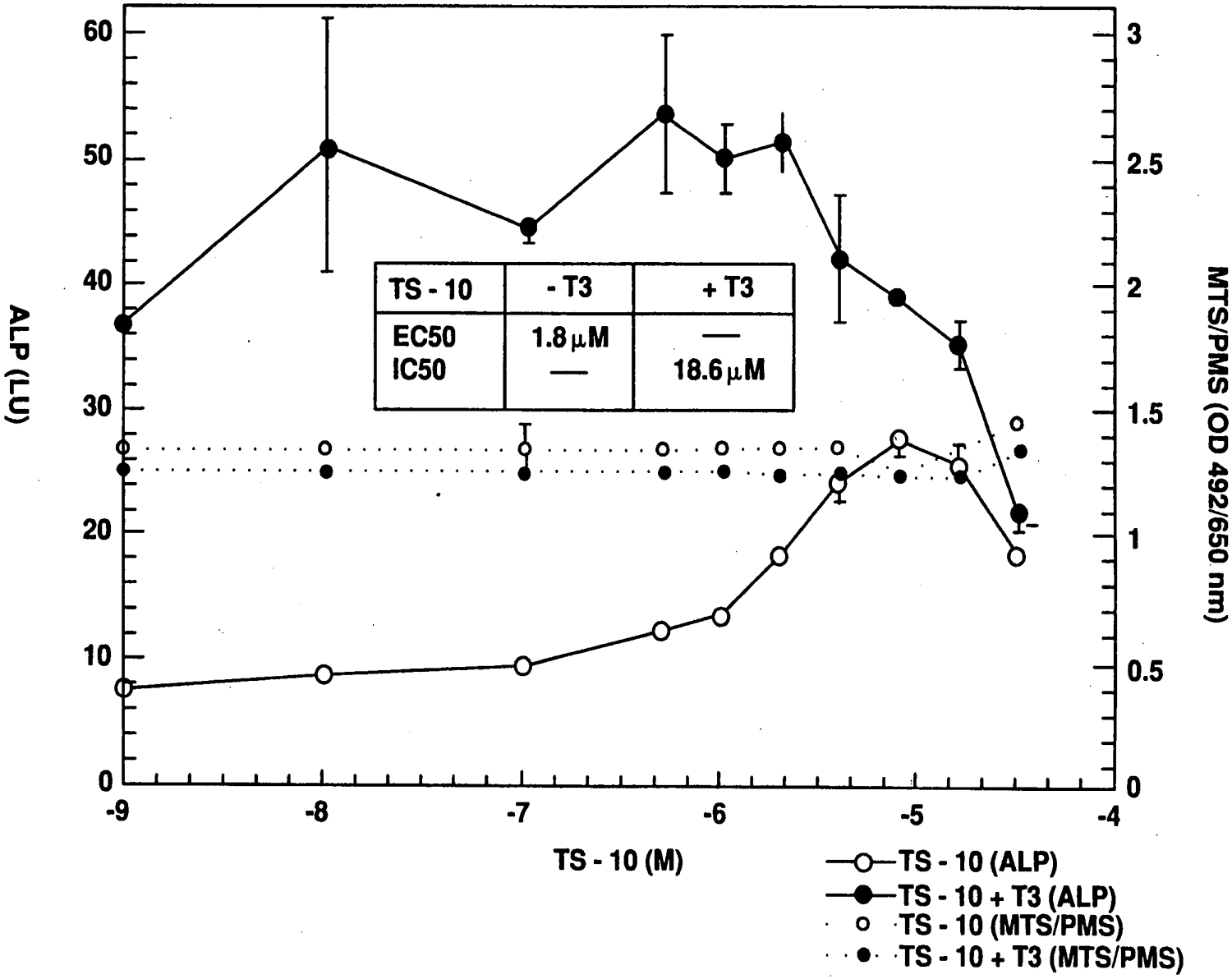

ALP (LU)
MTS/PMS (OD 492/650 nm)
TS - 10 (M)
TS - 10 | - T3 | + T3
EC50 | 1.8 μM | —
IC50 | — | 18.6 μM
TS - 10 (ALP)
TS - 10 + T3 (ALP)
TS - 10 (MTS/PMS)
TS - 10 + T3 (MTS/PMS)

FIG.19

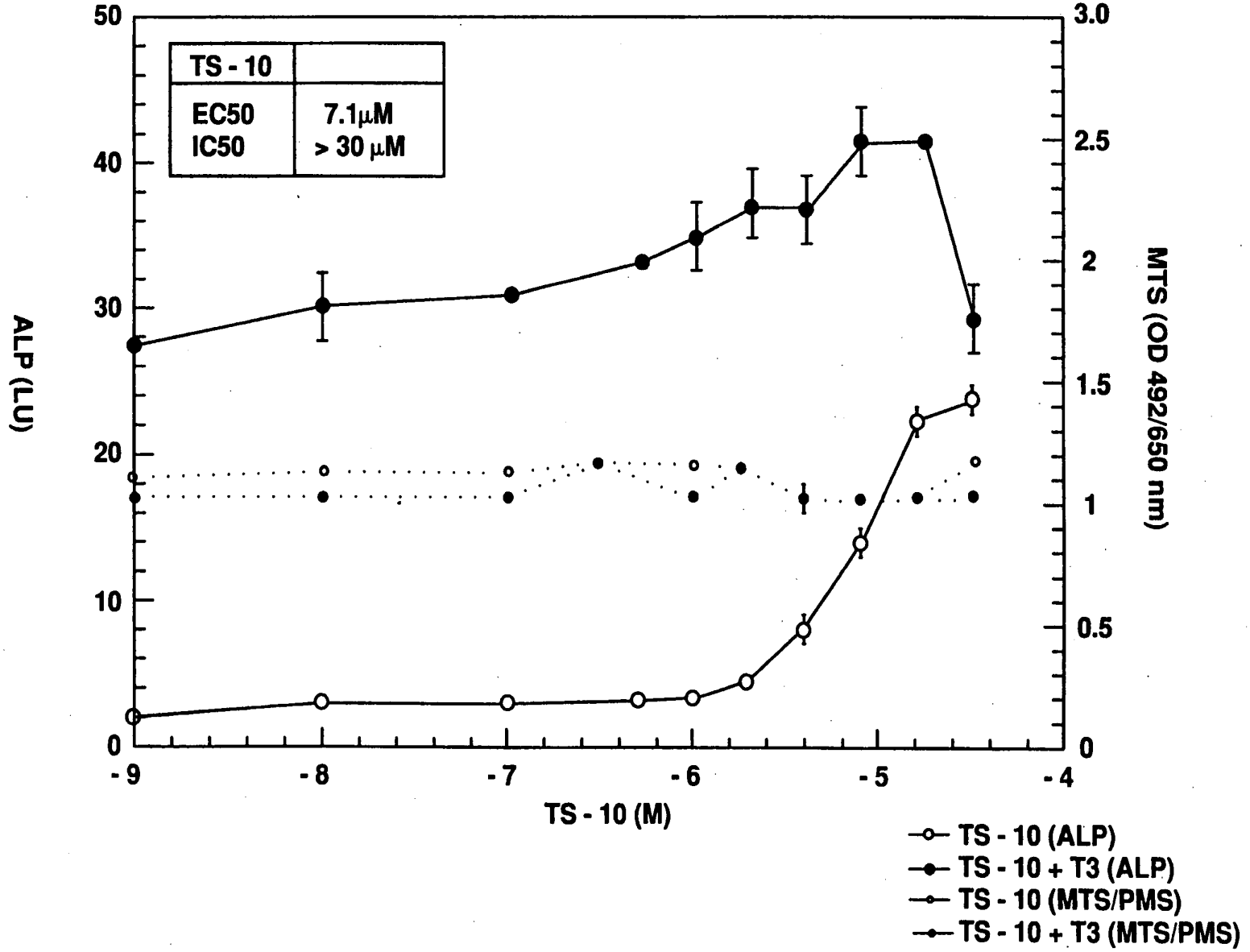
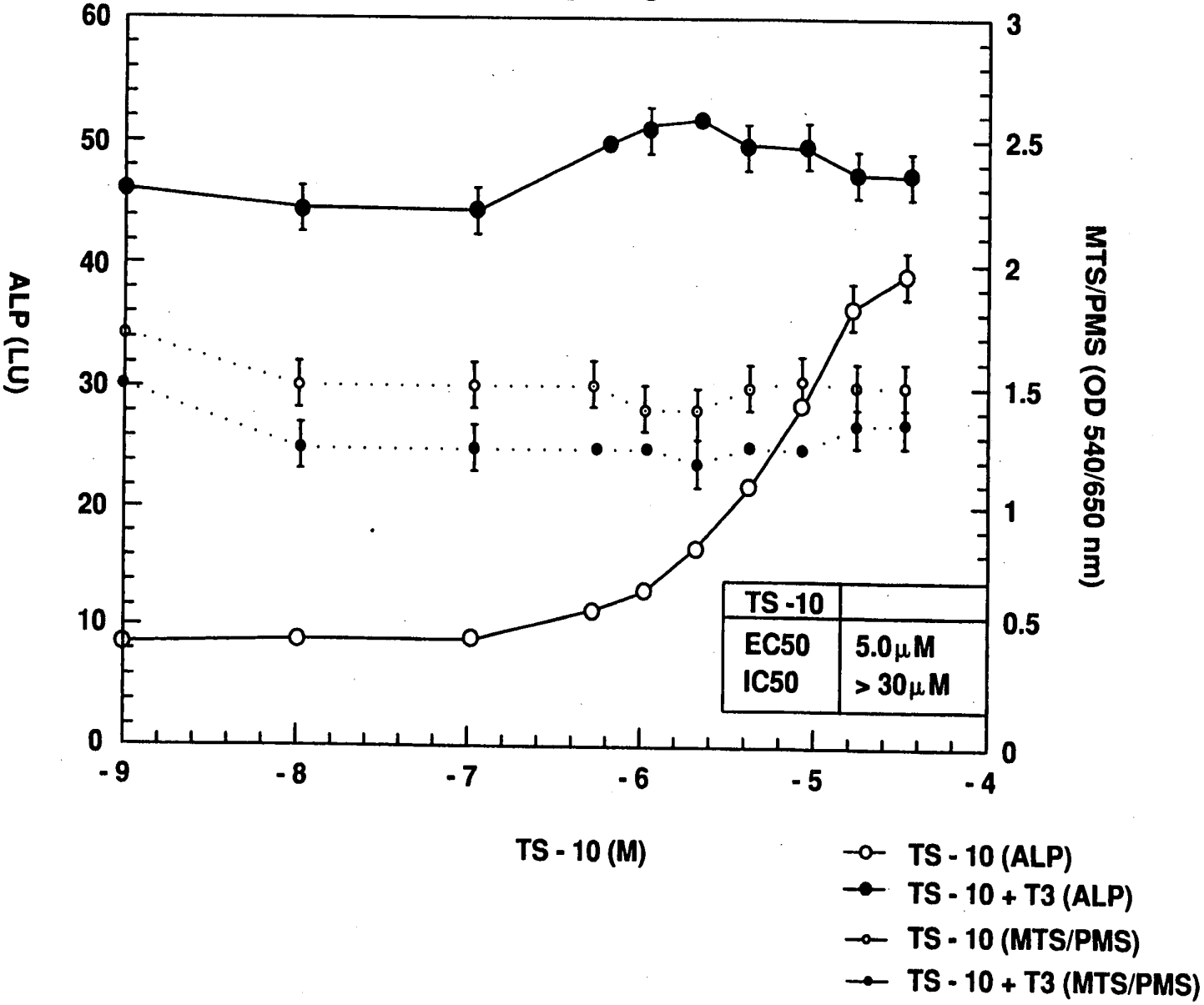

TS - 10
EC50 7.1μM
IC50 > 30 μM
ALP (LU)
MTS (OD 492/650 nm)
TS - 10 (M)
50
40
30
20
10
0
3.0
2.5
2
1.5
1
0.5
0
-9
-8
-7
-6
-5
-4
TS - 10 (ALP)
TS - 10 + T3 (ALP)
TS - 10 (MTS/PMS)
TS - 10 + T3 (MTS/PMS)

FIG.20


ALP (LU)
MTS/PMS (OD 540/650 nm)
TS - 10 (M)
60
50
40
30
20
10
0
3
2.5
2
1.5
1
0.5
0
-9
-8
-7
-6
-5
-4
TS -10
EC50
5.0μM
IC50
> 30μM
TS - 10 (ALP)
TS - 10 + T3 (ALP)
TS - 10 (MTS/PMS)
TS - 10 + T3 (MTS/PMS)

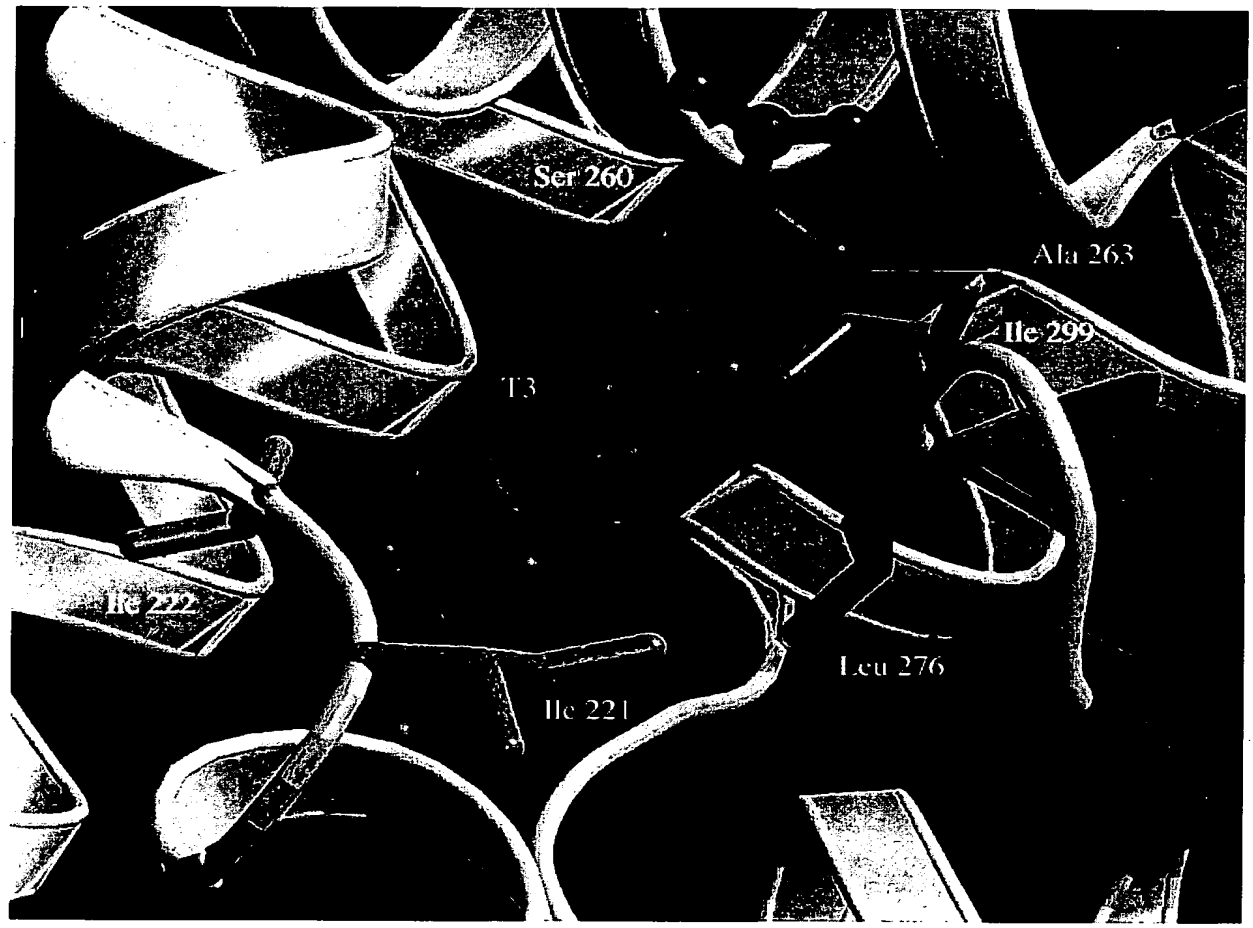


FIG. 21

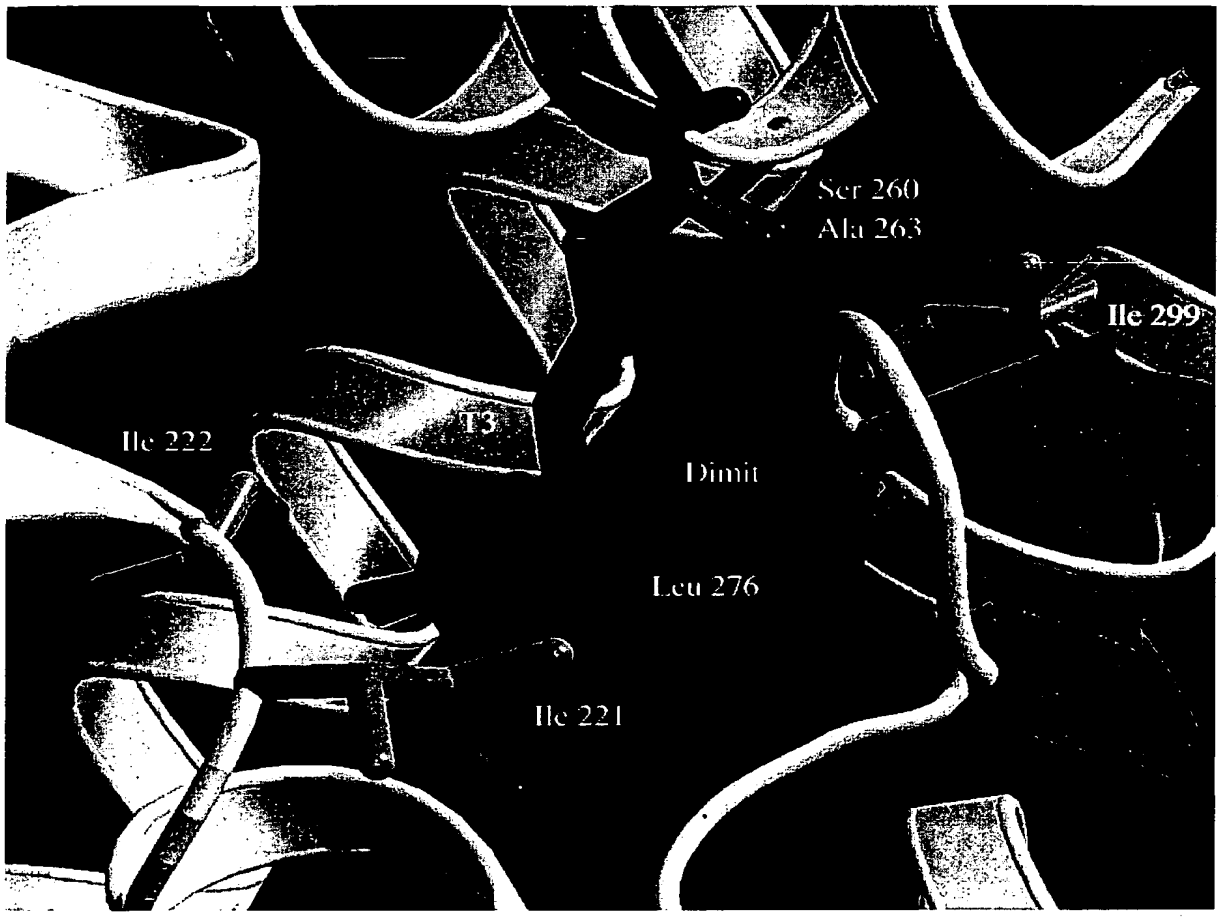


FIG. 22

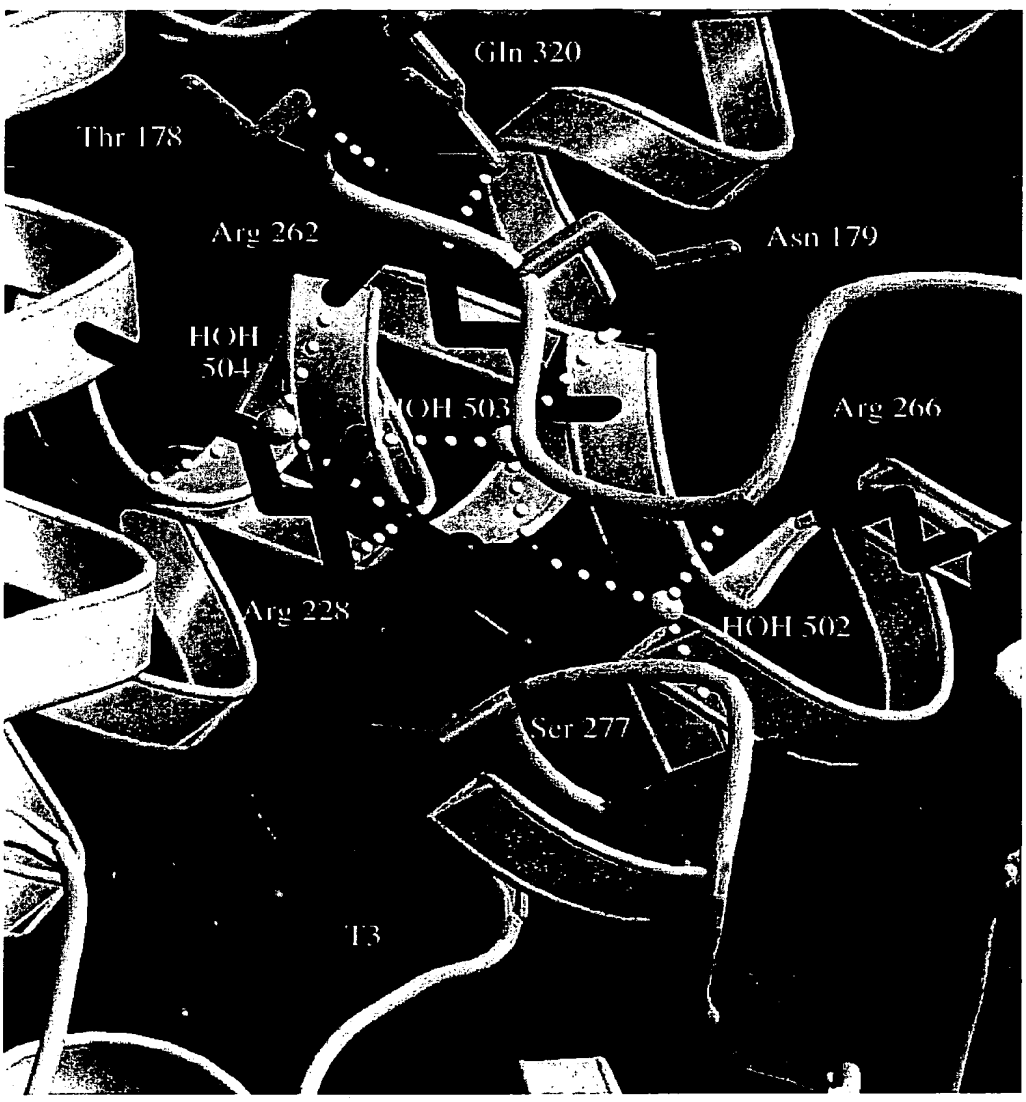

Gln 320
Thr 178
Arg 262
Asn 179
HOH
504
HOH 503
Arg 266
Arg 228
HOH 502
Ser 277
T3

FIG. 23


Gln 320
Thr 178
Arg 262
Asn 179
HOH
504
HOH 600
HOH 503
228
Arg 266
Ser 277
Triac

FIG. 24

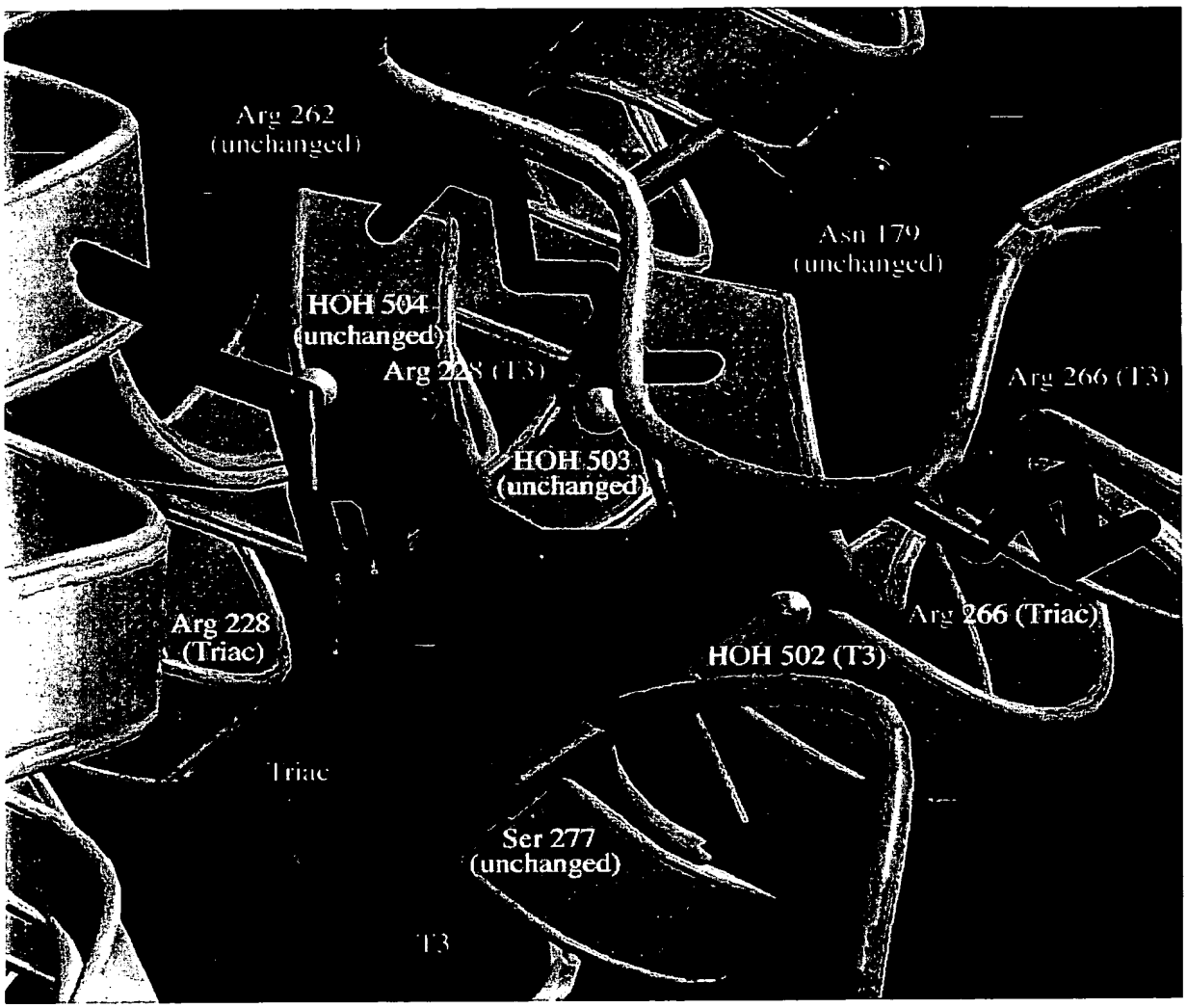

Arg 262
(unchanged)
Asn 179
(unchanged)
HOH 504
(unchanged)
Arg 228 (T3)
Arg 266 (T3)
HOH 503
(unchanged)
Arg 228
(Triac)
Arg 266 (Triac)
HOH 502 (T3)
Triac
Ser 277
(unchanged)
T3

FIG. 25


Arg262
Arg228
HOH504
HOH503
Met259
Ala263
Arg266
Phe405
HOH502
Ile299
Met256
His381
Ser277
Phe401
Leu276
Ile222
T3
Leu292
Met388
Ile221
Thr219
Phe218
Phe215

FIG. 26A

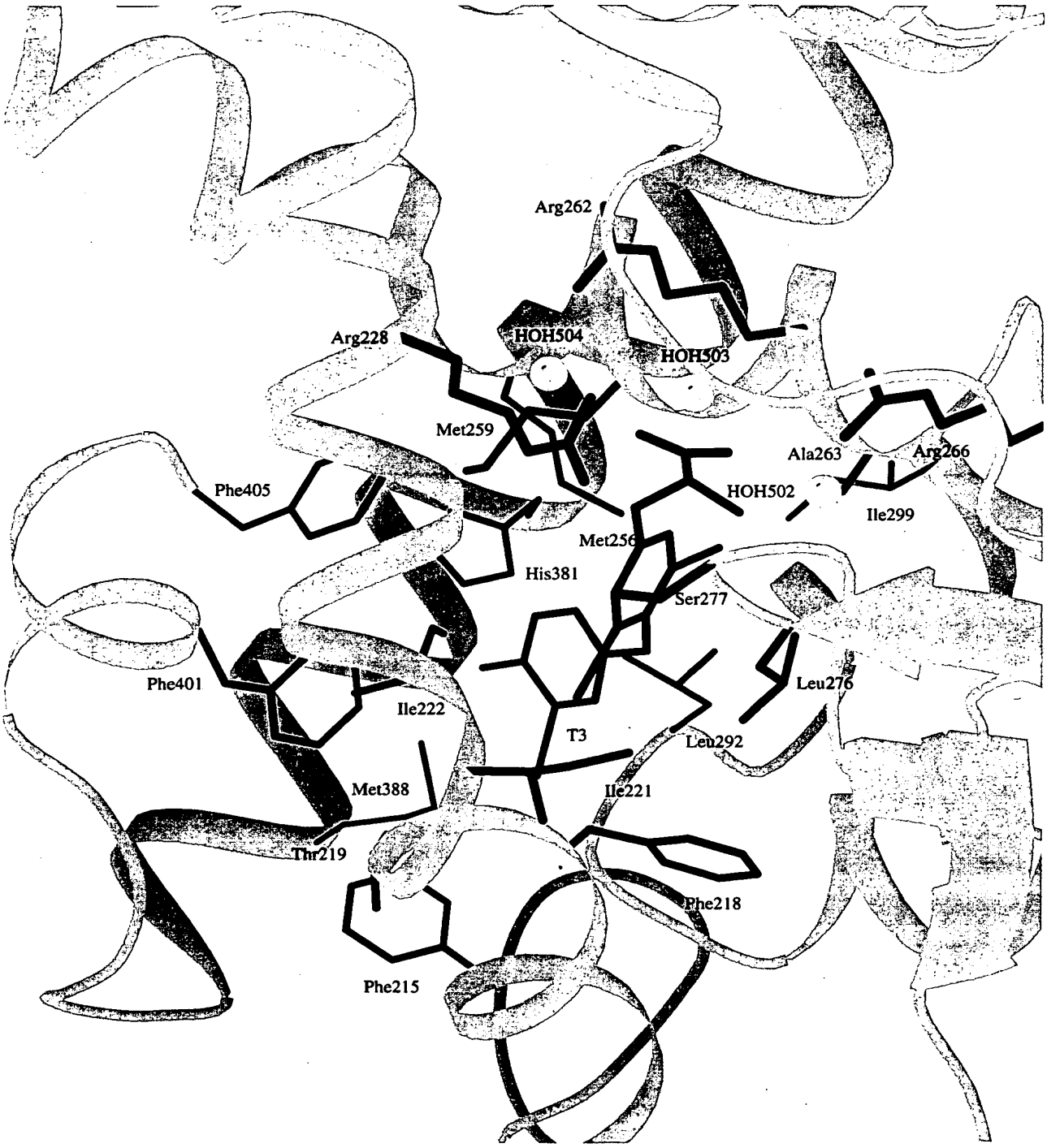

Arg262
Arg228
HOH504
HOH503
Met259
Ala263
Arg266
Phe405
HOH502
Ile299
Met256
His381
Ser277
Phe401
Leu276
Ile222
T3
Leu292
Met388
Ile221
Thr219
Phe218
Phe215

FIG. 26B

Thyroid Hormone Receptor Beta with GC1

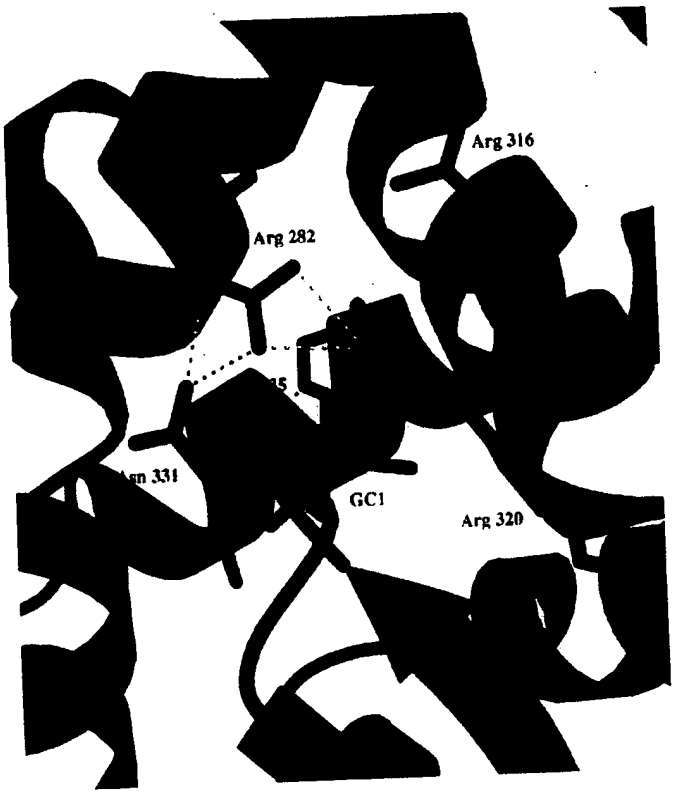


FIG. 27

Thyroid Hormone Receptor Beta with Triac

FIG. 28

Structural Differences Between TR-b with GC1 and TR-a with Dimit

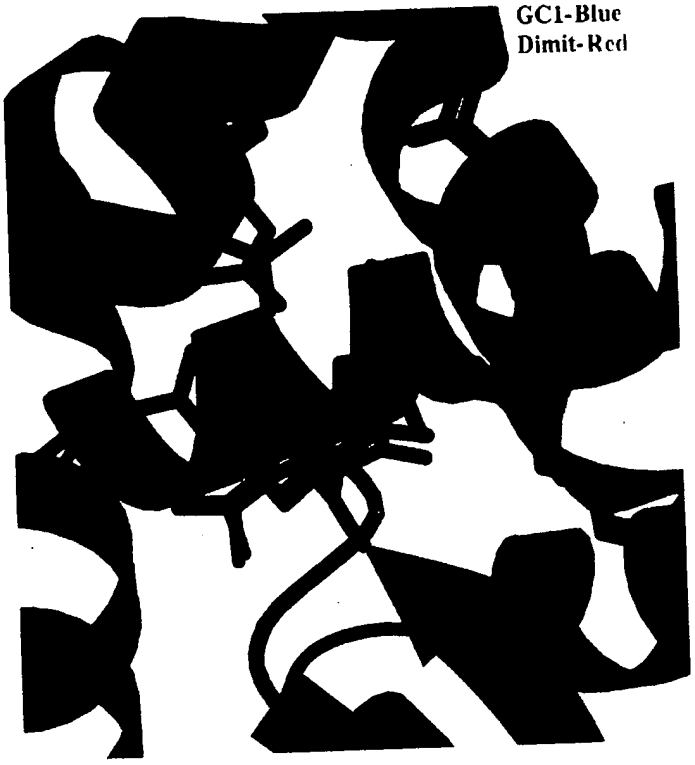


FIG. 29

Structural Differences between TR LBD isoforms with Triac

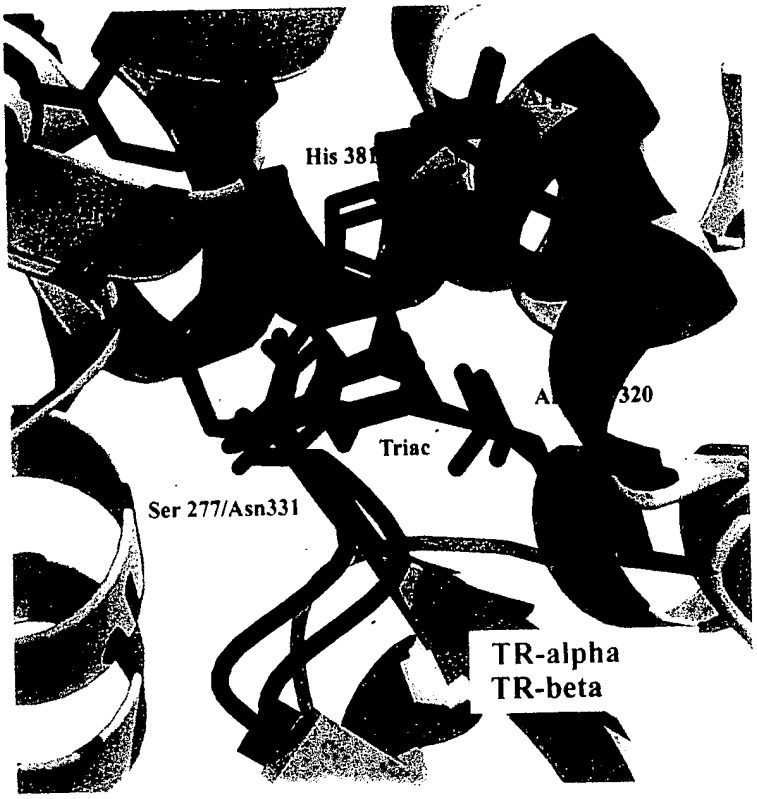
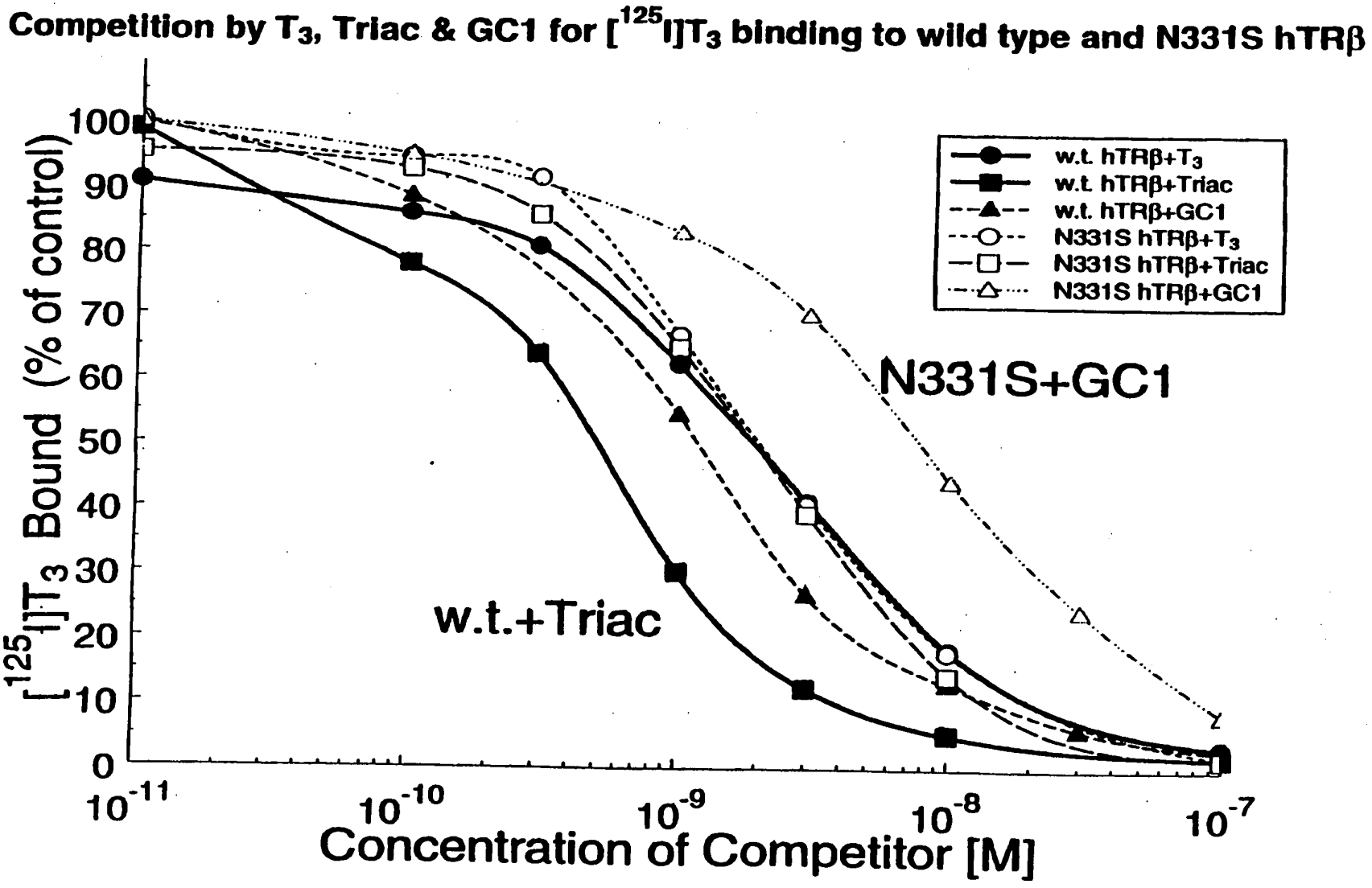
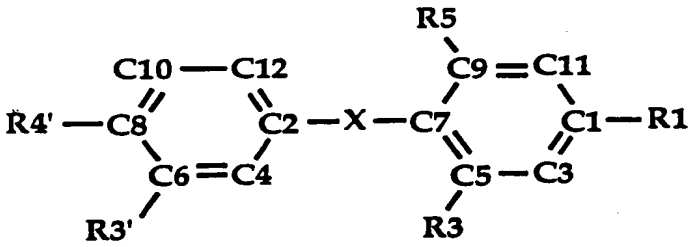


FIG. 30

FIG.31

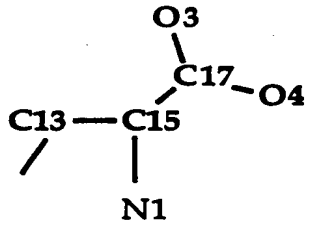

Competition by T_3, Triac & GC1 for [^{125}I]T_3 binding to wild type and N331S hTRβ
[^{125}I]T_3 Bound (% of control)
100
90
80
70
60
50
40
30
20
10
0
10^{-11}
10^{-10}
10^{-9}
10^{-8}
10^{-7}
Concentration of Competitor [M]
w.t. hTRβ+T_3
w.t. hTRβ+Triac
w.t. hTRβ+GC1
N331S hTRβ+T_3
N331S hTRβ+Triac
N331S hTRβ+GC1
N331S+GC1
w.t.+Triac

Atomic Numbering for Thyronine-like Ligands

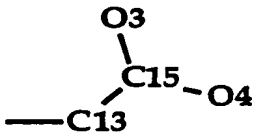


Ligand	R1	R3	R5	X	R3'	R4'
Dimit	amino propionic	C19	C20	O2	iPr	O1
$IpBr_2$	amino propionic	BR1	BR2	O2	iPr	O1
T_3	amino propionic	I1	I3	O2	I2	O1
Triac	acetic acid	I1	I3	O2	I2	O1
GC1	oxyacetic acid	C19	C20	C21	iPr	O1

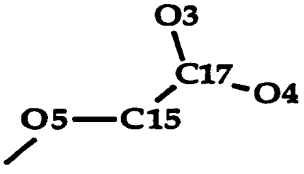
amino propionic acid



acetic acid



oxyacetic acid



isopropyl

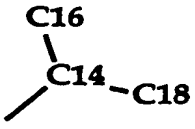


FIG.32